IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Kaneyoshi Kato et al.
Serial No. 10/089,951 Group Art Unit 1624
Filed September 27, 2002 Examiner LIU, HONG
For : AMINE DERIVATIVES

TRANSLATOR'S DECLARATION

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of the certified copy of Japanese Patent Application No. 286939/1999 filed on October 7, 1999; and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 30th day of June, 2004.

Ritsuko Arimura

(Translation)

P A T E N T O F F I C E

J A P A N E S E G O V E R N M E N T

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : October 7, 1999

Application Number : 286939/1999

Applicant(s) : Takeda Chemical Industries, Ltd.

Commissioner, Patent Office

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【Number of Claims】 16
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【Document】 Specification One copy
【Document】 Abstract One copy
【Number of General Power of Attorney】 9909276
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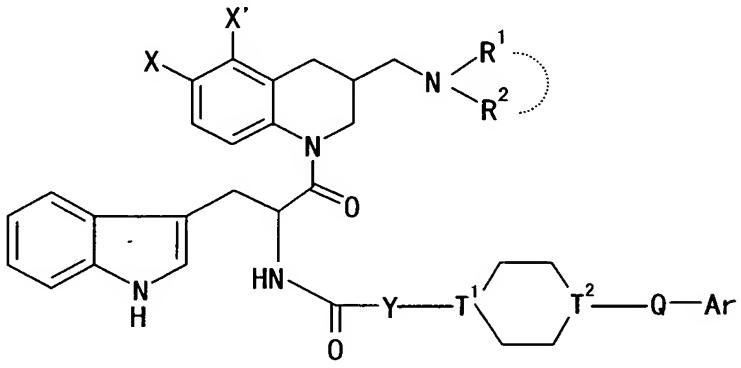
【Document】 SPECIFICATION

【Title of the Invention】 AMINE DERIVATIVES

【What is Claimed is】

【Claim 1】 A compound of the formula:



(I)

wherein X and X' are the same or different, and each represents a hydrogen atom, a fluorine atom or a chlorine atom, and at least one of X and X' represents a fluorine atom or a chlorine atom;

R^1 and R^2 represent a hydrogen atom or C_{1-6} alkyl optionally having substituents, or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring optionally having substituents;

Y and Q are the same or different, and each represents a bond or a spacer having a main chain of 1 to 6 atoms;

T^1 and T^2 are the same or different, and each represents CH or a nitrogen atom; and

Ar represents an aromatic group optionally having substituents;

provided that 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-(4-phenylpiperazin-1-yl)carbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline; 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidinocarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline and 1-benzoyl-N-[(R)-2-[6-chloro-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinolin-1-yl]-1-[3-

(indol-3-yl)propanoyl]-4-piperidinecarboxamide are excluded; or a salt thereof.

【Claim 2】 The compound according to claim 1, wherein X is a fluorine atom or a chlorine atom and X' is a hydrogen atom.

【Claim 3】 The compound according to claim 1, wherein R^1 and R^2 are each C_{1-6} alkyl.

【Claim 4】 The compound according to claim 1, wherein the spacer having a main chain of 1 to 6 atoms represented by Y and Q is a divalent group compring of 1 to 3 groups selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is a hydrogen atom, an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkyl-carbonyl, an optionally halogenated C_{1-6} alkylsulfonyl) and an optionally halogenated divalent C_{1-6} non-cyclic hydrocarbon group.

【Claim 5】 The compound according to claim 1, wherein Y is a bond or C_{1-2} alkylene.

【Claim 6】 The compound according to claim 1, wherein Q is -CO-.

【Claim 7】 The compound according to claim 1, wherein T^1 is CH and T^2 is a nitrogen atom.

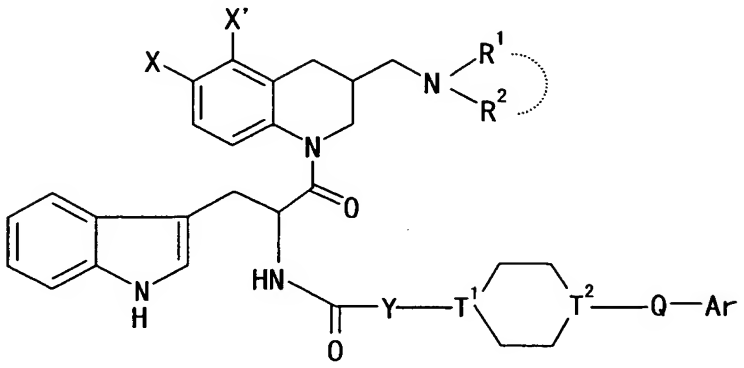
【Claim 8】 The compound according to claim 1, wherein Ar is a monocyclic aromatic group optionally having substituents.

【Claim 9】 The compound according to claims 1, wherein Ar is a fused aromatic group optionally having substituents.

【Claim 10】 The compound according to claim 8, wherein Ar is phenyl which may have 1 or 2 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl and an optionally halogenated C_{1-6} alkoxy.

【Claim 11】 A prodrug of the compound according to claims 1.

【Claim 12】 A pharmaceutical composition comprising a compound of the formula:



(I)

wherein X and X' are the same or different, and each represents a hydrogen atom, a fluorine atom or a chlorine atom, and at least one of X and X' represents a fluorine atom or a chlorine atom;

R^1 and R^2 represent a hydrogen atom or C_{1-6} alkyl optionally having substituents, or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring optionally having substituents;

Y and Q are the same or different, and each represents a bond or a spacer having a main chain of 1 to 6 atoms;

T^1 and T^2 are the same or different, and each represents CH or a nitrogen atom; and

Ar represents an aromatic group optionally having substituents;

provided that 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-(4-phenylpiperazin-1-yl)carbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline; 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidinocarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline and 1-benzoyl-N-[(R)-2-[6-chloro-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinolin-1-yl]-1-[3-(indol-3-yl)propanoyl]-4-piperidinecarboxamide are excluded; or a salt thereof, or a prodrug thereof.

【Claim 13】 The composition according to claim 12, which is a somatostatin receptor binding inhibitor.

【Claim 14】 The composition according to claim 13, which is a somatostatin subtype 2 receptor binding inhibitor.

【Claim 15】 The composition according to claim 13, which is a somatostatin receptor agonist.

【Claim 16】 The composition according to claim 15, which is a somatostatin subtype 2 receptor agonist.

【Detailed Description of the Invention】

【Technical Field to which the Invention Pertains】

The present invention relates to novel amine derivatives. In further detail, the present invention relates to a compound which has a somatostatin receptor binding inhibition activity, and is useful for preventing and/or treating diseases associated with somatostatin.

【Prior Art】

Somatostatin was found to be a growth hormone inhibiting factor (somatotropin release inhibiting factor; SRIF) in 1973.

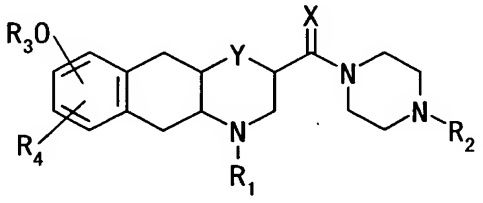
Somatostatin receptors were found to comprise five subtypes that have been named as SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5 respectively (e.g., Endocrinology, vol.136, pp.3695-3697, 1995; Trends in Pharmacological Sciences, pp.87-94, Vol.18, 1997; Life Science, Vol.57, pp.1249-1265, 1995).

Somatostatin is known to inhibit production and/or secretion of various hormones, growth factors, and physiologically active substances. As the hormones inhibited by somatostatin, mentioned are growth hormone (GH), thyroid-stimulating hormones (TSH), prolactin, insulin, and glucagon. Therefore, somatostatin has various functions in endocrine systems, exocrine systems and nerve systems, and drugs targeting somatostatin are being developed (e.g., Endocrinology, vol.136, p.3695-3697, 1995; Trends in Pharmacological Sciences, pp.87-94, vol.18, 1997).

Diseases caused by somatostatin include life-style related diseases such as diabetes; central nervous system diseases, immune system diseases, and hormone-dependent tumors. Trials to

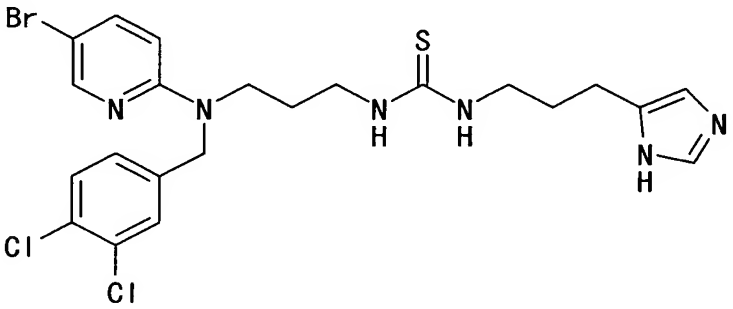
develop somatostatin itself or somatostatin analogues as a drug have been conducted. For instance, octreotide known as a somatostatin receptor agonist has been marketed as a drug for treating hormone-dependent tumors.

As a compound having a somatostatin receptor binding activity, especially a selective SSTR1 antagonist activity, there is known a compound represented by the formula:



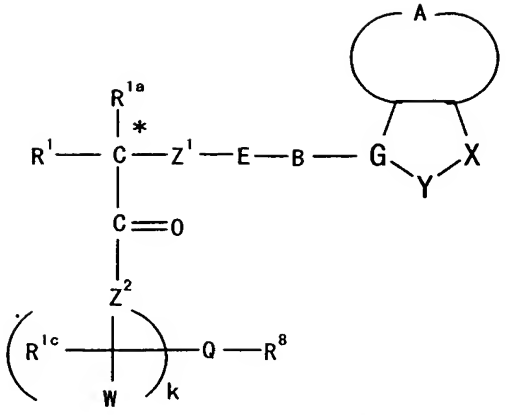
wherein X represents O or H, H; Y represents $-CH_2-$, $-O-$, $-NH-$ or $-S-$; R_1 represents H or C_{1-4} alkyl; R_2 represents H, benzyl, etc.; R_3 represents H, C_{1-4} alkyl, etc.; and R_4 represents hydrogen atom or halogen (WO97/03054).

As a compound which has a selective SSTR4 binding activity and is expected to have a glaucoma treating activity, there is known a compound represented by the formula:

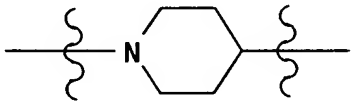


(J. Am. Chem. Soc., vol.120, pp.1368-1373, 1998; WO97/43278).

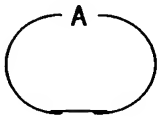
As a compound having a somatostatin receptor binding activity, especially a selective SSTR2 agonist activity, a compound represented by the formula:



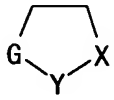
wherein R^1 represents C_{1-10}alkyl, etc.; R^{1a} represents H, etc.; Z^1 represents -O-, etc.; E represents $-SO_2-$, etc.; B represents



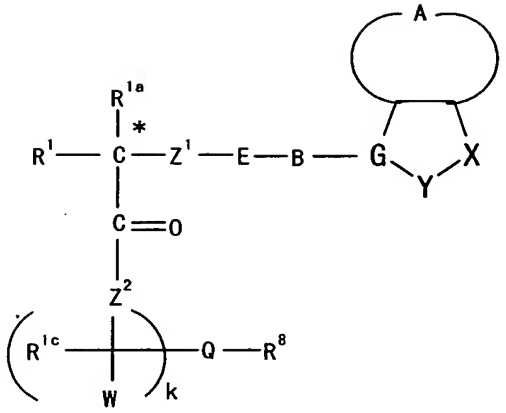
etc.;



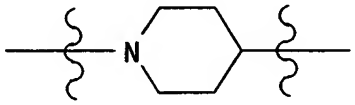
represents 5- or 6-membered aromatic or non-aromatic ring; G represents N, CH or C; Y represents -C(O)-, etc.; X represents -$N(R^{11})$- (R^{11} represents H, etc.), etc.;



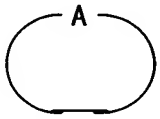
represents 5- to 10-membered condensed aryl, etc.; Z^2 represents -O-, etc.; R^{1c} represents H, etc.; W represents H, etc.; k represents 0 or 1; Q represents $-(CH_2)_x-V-(CH_2)_y-$ (x and y each represent 0, 1, 2, 3, 4, 5 or 6; V represents 6- to 12-membered aromatic monocyclic or bi-cyclic ring), etc.; and R^8 represents H, etc. (WO98/44921); and a compound represented by the formula:



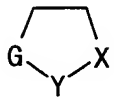
wherein R^1 represents C_{1-10} alkyl, etc.; R^{1a} represents H, etc.; Z^1 represents -O-, etc., E represents $-SO_2-$, etc.; B represents



etc.,



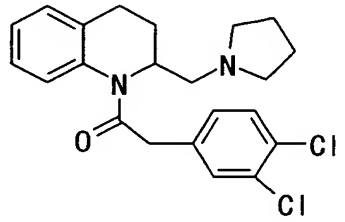
represents 5- or 6-membered aromatic or non-aromatic ring; G represents N, CH or C; Y represents -C(O)-, etc.; X represents $-N(R^{11})-$ (R^{11} represents H, etc.), etc.;



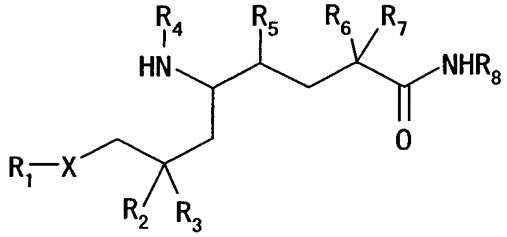
represents 5- to 10-membered condensed aryl, etc.; Z^2 represents -O-, etc.; R^{1c} represents H, etc.; W represents H, etc.; k represents 0 or 1; Q represents $-(CH_2)_x-V-(CH_2)_y-$ (x and y each represent 0, 1, 2, 3, 4, 5 or 6; V represents C_{3-10} saturated or partially saturated aromatic monocyclic or bi-cyclic ring containing 1 to 4 nitrogen atoms and 0 to 2 oxygen atoms or sulfur atoms), etc.; and R^8 represents H, etc.; (WO98/45285).

On the other hand, the following compounds are known as amine derivatives.

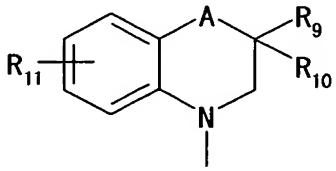
1) J. Med. Chem., vol.34, pp.2624-2633, 1991 describes, as a compound having a weak analgesic activity, a compound represented by the following formula:



2) JP-A-8-176087 describes 3-(N,N-dimethylaminomethyl)-1,2,3,4-tetrahydroquinoline as a synthetic intermediate for a compound represented by the formula:

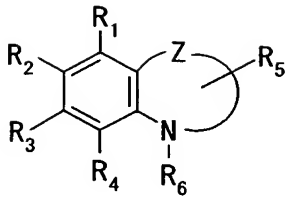


wherein R_1 represents arylamino such as



(A represents a direct bond, methylene, ethylene, imino, oxy or thio; R_9 represents C_{1-4} alkoxycarbonylamino-C_{1-4} alkyl, etc.; R_{10} represents hydrogen or C_{1-4} alkyl; R_{11} represents hydrogen or halogen; etc.); X represents carbonyl, etc.; R_2 and R_3 represent hydrogen, etc.; R_5 represents hydroxyl, etc.; R_6 represents hydrogen, etc.; R_7 represents hydrogen, etc.; R_8 represents aliphatic group, etc., which is described to be useful in the treatment of hypertension.

3) WO97/12860 describes, as a compound having an acyl-coenzyme A: cholesterol acyltransferase inhibiting activity and a lipid peroxidation inhibiting activity, a heterocyclic derivative represented by the formula:



wherein at least one of R_1, R_2 and R_5 represents alkyl or alkenyl which is substituted by hydroxy, an acidic group, alkoxycarbonyl or $-NR_9R_{10}$ (R_9 and R_{10} each represent hydrogen atom or lower alkyl), etc., and the remaining two groups independently represent hydrogen atom, lower alkyl or lower alkoxy; either R_2 or R_5 represents a group represented by the formula: $-NHCOR_7$ wherein R_7 represents alkyl, etc., and the remaining group represents hydrogen atom, lower alkyl or lower alkoxy; R_6 represents alkyl, alkenyl, alkoxyalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl or arylalkyl; Z represents nitrogen atom substituted by R_6, or a linker group forming 5-membered ring or 6-membered ring together with a carbon atom of benzene ring attached to the nitrogen atom and a carbon atom adjacent to the carbon atom, or a pharmaceutically acceptable salt thereof.

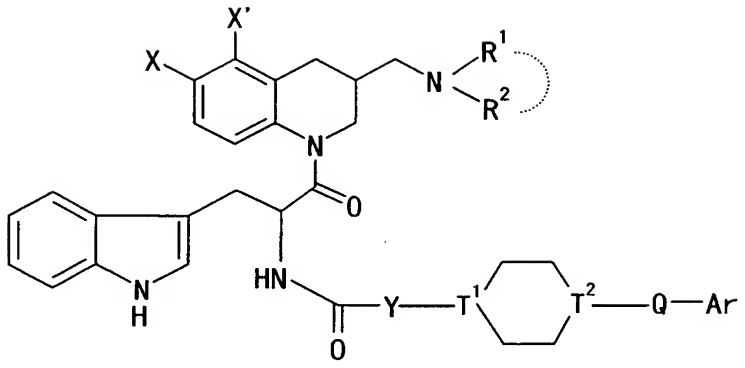
【Problems to be Solved by the Invention】

Conventional somatostatin and its analogues are all peptides. They are problematic in their oral absorbability, pharmacokinetics, etc. and are therefore unsatisfactory as medicines. It is desired to develop a compound which is different from conventional known compounds in its chemical structure, and which has a selective or nonselective affinity to somatostatin receptor subtypes, or an excellent somatostatin receptor binding inhibitory activity, etc., and which has satisfactory properties as a medicine.

【Means of Solving the Problems】

The present inventors have studied various compounds having a somatostatin receptor binding inhibitory activity, and, as a result, have found, for the first time, that a compound of the

formula:



(I)

wherein X and X' are the same or different, and each represents a hydrogen atom, a fluorine atom or a chlorine atom, and at least one of X and X' represents a fluorine atom or a chlorine atom;

R^1 and R^2 represent a hydrogen atom or C_{1-6} alkyl optionally having substituents, or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring optionally having substituents;

Y and Q are the same or different, and each represents a bond or a spacer having a main chain of 1 to 6 atoms;

T^1 and T^2 are the same or different, and each represents CH or a nitrogen atom; and

Ar represents an aromatic group optionally having substituents; provided that 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-(4-phenylpiperazin-1-yl)carbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline; 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidinocarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline and 1-benzoyl-N-[(R)-2-[6-chloro-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinolin-1-yl]-1-[3-(indol-3-yl)propanoyl]-4-piperidinecarboxamide are excluded; or a salt thereof [hereinafter sometimes referred to as compound (I)] has, based on its characteristic structure, an unexpectedly excellent somatostatin receptor binding inhibitory activity, and

that these compounds have low toxicity, etc and are therefore satisfactory as medicines. Based on these findings, the inventors have completed the present invention.

Specifically, the present invention relates to:

[1] a compound (I):

[2] the compound according to the above [1], wherein X is a fluorine atom or a chlorine atom and X' is a hydrogen atom;

[3] the compound according to the above [1], wherein R^1 and R^2 are each C_{1-6} alkyl;

[4] the compound according to the above [1], wherein the spacer having a main chain of 1 to 6 atoms represented by Y and Q is a divalent group comprising of 1 to 3 groups selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is a hydrogen atom, an optionally halogenated C_{1-6} alkyl, an optionally halogenated C_{1-6} alkyl-carbonyl, an optionally halogenated C_{1-6} alkylsulfonyl) and an optionally halogenated divalent C_{1-6} non-cyclic hydrocarbon group;

[5] the compound according to the above [1], wherein Y is a bond or C_{1-2} alkylene;

[6] the compound according to the above [1], wherein Q is -CO-;

[7] the compound according to the above [1], wherein T^1 is CH and T^2 is a nitrogen atom;

[8] the compound according to the above [1], wherein Ar is a monocyclic aromatic group optionally having substituents;

[9] the compound according to the above [1], wherein Ar is a fused aromatic group optionally having substituents;

[10] the compound according to the above [8], wherein Ar is phenyl which may have 1 or 2 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkyl and an optionally halogenated C_{1-6} alkoxy;

[11] a prodrug of the compound according the above [1];

[12] a pharmaceutical composition comprising compound (I);

[13] the composition according to the above [12], which is a

somatostatin receptor binding inhibitor;

[14] the composition according to the above [13], which is a somatostatin subtype 2 receptor binding inhibitor;

[15] the composition according to the above [13], which is a somatostatin receptor agonist;

[16] the composition according to the above [15], which is a somatostatin subtype 2 receptor agonist;

In the formula (I), X and X' are the same or different, they represent a hydrogen atom, a fluorine atom or a chlorine atom and at least one of X and X' represents a fluorine atom or a chlorine atom. More preferably, X represents a fluorine atom or a chlorine atom and X' represents a hydrogen atom.

In the formula (I), the "C_{1-6} alkyl" in the "C_{1-6} alkyl optionally having substituents" represented by R^1 and R^2 includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc. Among those, methyl, ethyl, propyl are preferred.

The "substituent" in said "C_{1-6} alkyl optionally having substituents" includes, for example, halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), optionally halogenated C_{1-6} alkylsulfonyl, formylamino, optionally halogenated C_{1-6} alkyl-

carboxamide, C_{1-6} alkoxy-carboxamide (e.g., methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propanoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), aromatic group optionally having substituents, etc. The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The above-mentioned "optionally halogenated C_{3-6} cycloalkyl" includes, for example, a C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) which may have 1 to 5, preferably, 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl, etc.

The above-mentioned "optionally halogenated C_{1-6} alkoxy" includes, for example, C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentyloxy, etc.) which may have 1 to 5, preferably, 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples are methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

The above-mentioned "optionally halogenated C_{1-6} alkylthio" includes, for example, C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) which may have 1 to 5, preferably, 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples are methylthio, difluoromethylthio,

trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc.

The above-mentioned "optionally halogenated C_{1-6} alkyl-carbonyl" includes, for example, C_{1-6} alkyl-carbonyl (e.g., acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, etc.) which may have 1 to 5, preferably, 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples are acetyl, monochloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, etc.

The above-mentioned "optionally halogenated C_{1-6} alkylsulfonyl" includes, for example, C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, etc.) which may have 1 to 5, preferably, 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples are methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.

The above-mentioned "optionally halogenated C_{1-6} alkyl-carboxamide" includes, for example, C_{1-6} alkylcarboxamide (e.g., acetamide, propanamide, butanamide, etc.) which may have 1 to 5, preferably, 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples are acetamide, trifluoroacetoamide, propanamide, and butanamide.

The above-mentioned "aromatic group optionally having substituents" is exemplified by one mentioned as the later-described Ar.

The "nitrogen-containing heterocyclic ring" for the "nitrogen-containing heterocyclic ring optionally having substituents" as formed by R^1 and R^2 together with the adjacent nitrogen atom includes, for example, 3- to 8-membered nitrogen-containing heterocyclic rings containing, in addition to carbon atoms, at least one nitrogen atom and optionally 1 to 3

heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms. Concretely mentioned are aziridine, azetidine, morpholine, thiomorpholine, piperidine, piperazine, pyrrolidine, hexamethyleneimine, heptamethyleneimine, hexahydropyrimidine, 1,4-diazepane, and unsaturated cyclic amines thereof (e.g., 1,2,5,6-tetrahydropyridine, etc.), etc. Among these, preferred are morpholine, piperidine, piperazine, pyrrolidine, etc.

The "substituent" in said "nitrogen-containing heterocyclic ring optionally having substituents" includes, for example, oxo, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl, C_{6-14} aryl optionally having substituents, C_{7-19} aralkyl optionally having substituents, C_{6-14} aryl-carbonyl optionally having substituents, 5- to 10-membered aromatic heterocyclic group optionally having substituents, etc. The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The above "optionally halogenated C_{1-6} alkyl" includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) which may have 1 to 5, preferably, 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples are methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

The "optionally halogenated C_{1-6} alkyl-carbonyl", "optionally halogenated C_{1-6} alkylsulfonyl" are exemplified by those mentioned as the "substituent" in the above "C_{1-6} alkyl optionally having substituents".

The "C_{6-14} aryl" in the "C_{6-14} aryl optionally having substituents" includes, for example, phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, and 2-anthryl. Among those, phenyl is preferred.

The "C_{7-19} aralkyl" in the "C_{7-19} aralkyl optionally having substituents" includes, for example, benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc. Among those, benzyl is preferred.

The "C_{6-14} aryl-carbonyl" in the "C_{6-14} aryl-carbonyl optionally having substituents" includes, for example, benzoyl, 1-naphthoyl, 2-naphthoyl, etc.

The "5- to 10-membered aromatic heterocyclic group" in the "5- to 10-membered aromatic heterocyclic group optionally having substituents" includes, for example, 5- to 10-membered (monocyclic or bicyclic) aromatic heterocyclic group containing, in addition to carbon atoms, preferably 1 to 4 of 1 or 2 kinds of heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms. Concretely, for example, 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isooxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl, etc.

The "substituents" of the above "C_{6-14} aryl optionally having substituents", "C_{7-19} aralkyl optionally having substituents", "C_{6-14} aryl-carbonyl optionally having substituents" and "5- to 10-membered aromatic heterocyclic group optionally having substituents" includes, for example, halogen atoms (e.g.,

fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C_{1-6} alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), optionally halogenated C_{1-6} alkylsulfonyl, formylamino, optionally halogenated C_{1-6} alkylcarboxamide, C_{1-6} alkoxy-carboxamide (e.g., methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propanoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), etc. The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The "optionally halogenated C_{1-6} alkyl" is exemplified by those mentioned as the "substituent" in the above "nitrogen-containing heterocyclic ring optionally having substituents".

The "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio", "optionally halogenated C_{1-6} alkyl-carbonyl", "optionally

halogenated C_{1-6} alkylsulfonyl" and "optionally halogenated C_{1-6} alkyl-carboxamide" are exemplified by those mentioned as the "substituent" in the above "C_{1-6} alkyl optionally having substituents".

For R^1 and R^2, preferred are C_{1-6} alkyl, more preferred are methyl, ethyl and propyl; the most preferred is methyl.

In the formula (I), the "spacer having a main chain of 1 to 6 atoms" represented by Y and Q means a spacer in which 1 to 6 atoms of a main chain are combined in a straight-chain form. The "number of atoms of a main chain" is counted so as the number of atoms of the main chain is minimum.

The "spacer having a main chain of 1 to 6 atoms" includes, for example, divalent group comprising 1 to 3 groups selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is hydrogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl) and optionally halogenated divalent C_{1-6} non-cyclic hydrocarbon group.

The "optionally halogenated C_{1-6} alkyl" is exemplified by those mentioned as the "substituent" in the above "nitrogen-containing heterocyclic ring optionally having substituents".

The "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl" are each exemplified by those mentioned as the "substituent" in the above-mentioned "C_{1-6} alkyl optionally having substituents".

The "divalent C_{1-6} non-cyclic hydrocarbon group" in the "optionally halogenated divalent C_{1-6} non-cyclic hydrocarbon group" includes, for example,

(1) C_{1-6} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CF_3)-$, $-(CH(CH_3))_2-$, $-(CF_2)_2-$, $-(CH_2)_2\ C(CH_3)_2-$, $-(CH_2)_3\ C(CH_3)_2-$, etc.);

(2) C_{2-6} alkenylene (e.g., $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CF=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, etc.);

(3) C_{2-6} alkynylene (e.g., $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.);

each of which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), etc.

The preferable examples of said "spacer having a main chain of 1 to 6 atoms" are

(1) C_{1-6} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CHCH_3-$, $-C(CH_3)_2-$, $-CH(CF_3)-$, $-(CH(CH_3))_2-$, $-(CF_2)_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, etc.);

(2) C_{2-6} alkenylene (e.g., $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CF=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, etc.);

(3) C_{2-6} alkynylene (e.g., $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.);

(4) $-(CH_2)_{w1}O(CH_2)_{w2}-$, $-(CH_2)_{w1}S(CH_2)_{w2}-$, $-(CH_2)_{w1}CO(CH_2)_{w2}-$, $-(CH_2)_{w1}SO(CH_2)_{w2}-$, $-(CH_2)_{w1}SO_2\ (CH_2)_{w2}-$, $-(CH_2)_{w1}NR^8\ (CH_2)_{w2}-$;

(5) $-(CH_2)_{w3}CO\ NR^8\ (CH_2)_{w4}-$, $-(CH_2)_{w3}NR^8CO(CH_2)_{w4}-$, $-(CH_2)_{w3}SO_2\ NR^8(CH_2)_{w4}-$, $-(CH_2)_{w3}\ NR^8SO_2\ (CH_2)_{w4}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$;

(6) $-(CH_2)_{w5}\ NR^8CO\ NR^{8b}(CH_2)_{w6}-$;

(R^8 has the same meanings as above; R^{8b} has the same meanings as R^8; w1 and w2 represent an integer of 0 to 5 and w1 + w2 represents 0 to 5; w3 and w4 represent an integer of 0 to 4 and w3 + w4 represents 0 to 4; w5 and w6 represent an integer of 0 to 3 and w5 + w6 represents 0 to 3)

The "spacer having a main chain of 1 to 6 atoms" represented by Y is, more preferably, C_{1-2} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, etc.), etc.

The "spacer having a main chain of 1 to 6 atoms" represented Q is, more preferably, $-(CH_2)_{w1}CO(CH_2)_{w2}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (the symbols have the same meanings as above), etc.

Y represents, preferably, a bond or C_{1-2} alkylene (e.g., -

CH_2-, $-(CH_2)_2-$, etc.), etc.

Q represents, preferably, a bond, $-(CH_2)_{w1}CO(CH_2)_{w2}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (the symbols have the same meanings as above), etc. Among those, -CO- is particularly preferred.

In the formula (I), T^1 and T^2 are the same or different and represent CH or a nitrogen atom and preferred is the case in which T^1 is CH and T^2 is a nitrogen atom.

In the formula (I), the "aromatic group" in the "aromatic group optionally having substituents" includes, for example, monocyclic aromatic group, fused aromatic group, aromatic ring assembly group, etc.

Said monocyclic aromatic group includes, for example, a monovalent group which is derived by removing an optional hydrogen atom from monocyclic aromatic group. The "monocyclic aromatic ring" includes, for example, benzene and a 5- or 6-membered aromatic heterocyclic ring.

The "5- or 6-membered aromatic heterocyclic ring" includes, for example, 5- or 6-membered aromatic heterocyclic rings containing, in addition to carbon atoms, one or more (e.g., 1 to 3) heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, etc. Concretely mentioned are thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazane, etc.

The concrete examples of "monocyclic aromatic group" are phenyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 3- or 4-pyrazolyl, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 4-imidazolyl, 3- or 4-pyridazinyl, 3-isothiazolyl, 3-isooxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, etc.

The "fused aromatic group" includes, for example, a monovalent group derived by removing an optional hydrogen atom from a fused polycyclic (preferably bi- to tetra-cyclic,

preferably bi- or tri-cyclic) aromatic ring. The "fused polycyclic aromatic ring" includes, for example, a fused polycyclic aromatic hydrocarbon, a fused polycyclic aromatic heterocyclic ring, etc.

Said "fused polycyclic aromatic hydrocarbon" includes, for example, a C_{9-14} fused polycyclic (bi- or tri-cyclic) aromatic hydrocarbon (e.g., naphthalene, indene, fluorene, anthracene, etc.), etc.

Said "fused polycyclic aromatic heterocyclic ring" includes, for example, 9- to 14-membered, preferably 9- or 10-membered fused polycyclic aromatic heterocyclic rings containing, in addition to carbon atoms, one or more (e.g., 1 to 4) heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, etc. The concrete examples of "fused polycyclic aromatic heterocyclic ring" are benzofuran, benzothiophene, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiazine, phenoxazine, phthalazine, naphthyridine, quinazoline, cinnoline, carbazole, β-carboline, acridine, phenadine, phthalimido, etc.

Specific examples of the "fused aromatic group" includes, for example, 1-naphthyl; 2-naphthyl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzothienyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; etc.

The "aromatic ring assembly group" includes, for example, a group derived by removing an optional hydrogen atom from aromatic ring assemblies in which two or more, preferably two or three aromatic rings are directly connected with each other by single bond(s) and the number of such direct ring junctions is one less than the number of the aromatic rings involved.

The above-mentioned aromatic ring assemblies include, for

example, aromatic ring assemblies formed by two or three (preferably two) groups selected from a C_{6-14} monocyclic or fused polycyclic aromatic hydrocarbon (e.g., benzene ring, naphthalene ring, etc.) and 5- to 10-membered (preferably 5- or 6-membered) aromatic heterocyclic rings.

Preferred examples of the aromatic ring assemblies include one composed of two or three aromatic rings selected from the group consisting of benzene, naphthalene, pyridine, pyrimidine, thiophene, furan, thiazole, isothiazole, oxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, quinoline, isoquinoline, indole, benzothiophene, benzoxazole, benzothiazole, and benzofuran.

As specific examples of the "aromatic ring assembly group", mentioned are 2-, 3- or 4-biphenylyl; 3-(1-naphthyl)-1,2,4-oxadiazol-5-yl; 3-(2-naphthyl)-1,2,4-oxadiazol-5-yl; 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl; 3-phenyl-1,2,4-oxadiazol-5-yl; 3-(2-benzoxazolyl)-1,2,4-oxadiazol-5-yl; 3-(3-indolyl)-1,2,4-oxadiazol-5-yl; 3-(2-indolyl)-1,2,4-oxadiazol-5-yl; 4-phenylthiazol-2-yl; 4-(2-benzofuranyl)thiazol-2-yl; 4-phenyl-1,3-oxazol-5-yl; 5-phenyl-isothiazol-4-yl; 5-phenyloxazol-2-yl; 4-(2-thienyl)phenyl; 4-(3-thienyl)phenyl; 3-(3-pyridyl)phenyl; 4-(3-pyridyl)phenyl; 6-phenyl-3-pyridyl; 5-phenyl-1,3,4-oxadiazol-2-yl; 4-(2-naphthyl)phenyl; 4-(2-benzofuranyl)phenyl; 4,4'-terphenyl; etc.

Among the "aromatic group" described in the above, preferred is "monocyclic aromatic group" and "fused aromatic group".

Said "monocyclic aromatic group" is, preferably, phenyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl.

Said "fused aromatic group" is, preferably, fused polycyclic aromatic heterocyclic group and more preferably, 2-benzothienyl, 2-benzofuranyl, indol-2-yl, indol-3-yl.

The "substituent" in the "aromatic group optionally having substituents" represented by Ar includes, for example, oxo,

halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, C_{6-14} aryloxy-C_{1-6} alkyl (e.g., phenoxymethyl, etc.), C_{1-6} alkyl-C_{6-14} aryl-C_{2-6} alkenyl (e.g., methylphenylethenyl, etc.), optionally halogenated C_{3-6} cycloalkyl, C_{7-19} aralkyl optionally having substituents, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, C_{6-14} aryloxy optionally having substituents, C_{7-19} aralkyloxy optionally having substituents, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), 5- to 7-membered saturated cyclic amino optionally having substituents, acyl, acylamino, acyloxy, etc.

The "aromatic group" represented by Ar may have 1 to 5, preferably 1 to 3 of the above substituents at substitutable positions on the aromatic group. When the number of the substituents is two or more, those substituents may be the same or different.

The "optionally halogenated C_{1-6} alkyl" and "C_{7-19} aralkyl optionally having substituents" are exemplified by those mentioned as the "substituent" in the above "nitrogen-containing heterocyclic ring optionally having substituents".

The "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio" are exemplified by those mentioned as the "substituent" in the above "C_{1-6} alkyl optionally having substituents".

The "C_{6-14} aryloxy" in the "C_{6-14} aryloxy optionally having substituents" mentioned above includes, for example, phenyloxy, 1-naphthyloxy, 2-naphthyloxy, etc.

The "C_{7-19} aralkyloxy" in the "C_{7-19} aralkyloxy optionally having substituents" mentioned above includes, for example,

benzyloxy, phenethyloxy, diphenylmethyloxy, triphenylmethyloxy, 1-naphthylmethyloxy, 2-naphthylmethyloxy, 2,2-diphenylethyloxy, 3-phenylpropyloxy, 4-phenylbutyloxy, 5-phenylpentyloxy, etc.

The "substituents" in the "C_{6-14} aryloxy optionally having substituents" and "C_{7-19} aralkyloxy optionally having substituents" are exemplified by those mentioned as the "substituent" in the above "C_{6-14} aryl optionally having substituents". The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The "5- to 7-membered saturated cyclic amino" for the above "5- to 7-membered saturated cyclic amino optionally having substituents" includes, for example, morpholino, thiomorpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, etc. The "5- to 7-membered saturated cyclic amino" may be condensed with benzene ring.

The "substituent" in said "5- to 7-membered saturated cyclic amino" is exemplified by those mentioned as the "substituent" in the above "nitrogen-containing heterocyclic ring optionally having substituents". The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The "acyl" mentioned above includes, for example, an acyl represented by the following formulas: $-CO-R^3$, $-CO-OR^3$, $-CO-NR^3R^4$, $-CS-NR^3R^4$, $-SO_2-R^{3a}$ and $-SO-R^{3a}$

wherein R^3 is (i) hydrogen atom, (ii) hydrocarbon group optionally having substituents, or (iii) heterocyclic group optionally having substituents;

R^{3a} is (i) hydrocarbon group optionally having substituents, or (ii) heterocyclic group optionally having substituents;

R^4 represents hydrogen atom or C_{1-6} alkyl;

R^3 and R^4, taken together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring optionally

having substituents.

The "hydrocarbon group" represented by R^3 and R^{3a} in the "hydrocarbon group optionally having substituents" include, for example, chain or cyclic hydrocarbon group such as alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, etc. Among them, the following C_{1-19} chain or cyclic hydrocarbon groups are preferable:

a) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.),

b) C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, 2-butenyl, etc.),

c) C_{2-6} alkynyl (e.g., ethynyl, propargyl, 2-butynyl, etc.),

d) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), and C_{3-6} cycloalkyl being optionally condensed with one benzene ring,

e) C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl, etc.), preferably phenyl,

f) C_{7-19} aralkyl (e.g., benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.), preferably benzyl.

The "substituent" in the "hydrocarbon group optionally having substituents" includes, for example, halogen atoms, (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), 5- to 7-membered saturated cyclic amino optionally having substituents, formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C_{6-14}

aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), 5- or 6-membered heterocyclic carbonyl (e.g., nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, piperidinocarbonyl, pyrrolidin-1-ylcarbonyl, etc.), C_{6-14} aryloxy-carbonyl (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl, etc.), C_{7-19} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, diphenylmethyloxycarbonyl, triphenylmethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 2,2-diphenylethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl, 5-phenylpentyloxycarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, etc.), 5- or 6-membered heterocyclic carbamoyl (e.g., morpholinocarbamonyl, piperidinocarbamoyl, 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), optionally halogenated C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.), formylamino, optionally halogenated C_{1-6} alkyl-carboxamide, C_{6-14} aryl-carboxamide (e.g., phenylcarboxamide, naphthylcarboxamide, etc.), C_{1-6} alkoxy-carboxamide (e.g., methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g., methylsulfonylaminol, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propanoyloxy, etc.), C_{6-14} aryl-carbonyloxy (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), 5- or 6-membered heterocyclic

carbonyloxy (e.g., nicotinoyloxy, etc.), C_{6-14} aryloxy (e.g., phenoxy, naphthoxy, etc.), etc. The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio", "optionally halogenated C_{1-6} alkyl-carbonyl", "optionally halogenated C_{1-6} alkylsulfonyl" and "optionally halogenated C_{1-6} alkyl-carboxamide" are exemplified by those mentioned as the "substituent" in the above "C_{1-6} alkyl optionally having substituents".

The "5- to 7-membered saturated cyclic amino optionally having substituents" is exemplified by those mentioned as the "substituent" in the above "aromatic group optionally having substituents".

The "heterocyclic group" in the "heterocyclic group optionally having substituents" represented by R^3 or R^{3a} includes, for example, a monovalent group derived by removing an optional hydrogen atom from 5- to 14-membered (monocyclic, di- or tri-cyclic) heterocyclic rings containing, in addition to carbon atoms, 1 to 4 of 1 or 2 kinds of heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, etc., preferably (i) aromatic heterocyclic rings, (ii) 5- to 10-membered non-aromatic heterocyclic rings, and (iii) 7- to 10-membered bridged heterocyclic rings.

The "aromatic heterocyclic ring" includes, for example, 5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic rings containing, in addition to carbon atoms, one or more (e.g., 1 to 4) heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, etc. Concretely mentioned is an aromatic heterocyclic ring such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isooxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-

thiadiazole, 1,3,4-thiadiazole, furazan, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, phenoxathine, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazinephenothiazine, phenoxazine, phthalimide, etc.; and a ring as formed through condensation of the above ring, preferably monocyclic ring, with one or more, preferably one or two aromatic rings (e.g., benzene ring, etc.), etc.

The above-mentioned "5- to 10-membered non-aromatic heterocyclic rings" includes, for example, 2- or 3- pyrroline, pyrrolidine, 2- or 3-imidazoline, 2-oxazoline, oxazolidine, 2- or 3-pyrazoline, pyrazolidine, 2-thiazoline, piperidine, piperazine, hexamethyleneimine, morpholine, thiomorpholine, etc.

The above-mentioned "7- to 10-membered bridged heterocyclic ring" includes, for example, quinuclidine, 7-azabicyclo[2.2.1]heptane, etc.

Said "heterocyclic group" is preferably 5- to 10-membered (monocyclic or dicyclic) heterocyclic groups containing, in addition to carbon atoms, preferably 1 to 4 of 1 or 2 kinds of heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, etc. Concretely mentioned are aromatic heterocyclic groups such as 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1- 3- or 4-pyrazolyl; 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isooxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 3-, 4-, 5- or 6-benzothienyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; etc; non-aromatic heterocyclic

group such as 1-, 2- or 3-pyrrolidinyl; 1-, 2- 4- or 5-imidazolidinyl; 2- or 4-imidazolinyl; 2-, 3- or 4-pyrazolydinyl; piperidino; 2-, 3- or 4-piperidyl; 1- or 2-piperazinyl; morpholino; thiomorpholino; etc.

The "substituent" in the "heterocyclic group optionally having substituents" is exemplified by those mentioned as the "substituent" in the above "C_{6-14} aryl optionally having substituents". The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The "C_{1-6} alkyl" represented by R^4 include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

For the "nitrogen-containing heterocyclic ring optionally having substituents" formed by R^3 and R^4 together with the adjacent nitrogen atom, those similar to the nitrogen-containing heterocyclic ring optionally having substituents formed by R^1 and R^2 as mentioned above can be used.

Said "acyl" is, preferably, formyl, carboxy, carbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C_{6-14} aryl-carbonyl optionally having substituents (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C_{6-14} aryloxy-carbonyl optionally having substituents (e.g., phenoxycarbonyl, etc.), C_{7-19} aralkyloxy-carbonyl optionally having substituents (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), 5- or 6-membered heterocyclic carbonyl optionally having substituents (e.g., nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, piperidinocarbonyl, pyrrolidin-1-ylcarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl optionally having substituents (e.g.,

phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), 5- or 6-membered heterocyclic carbamoyl optionally having substituents (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), optionally halogenated C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl optionally having substituents, etc. and more preferably, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl optionally having substituents, C_{6-14} arylsulfonyl optionally having substituents (e.g., benzenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl, etc.), etc.

Furthermore, the "substituent" in the "C_{6-14} aryl-carbonyl optionally having substituents", "C_{6-14} aryloxy-carbonyl optionally having substituents", "C_{7-19} aralkyloxy-carbonyl optionally having substituents", "5- or 6-membered heterocyclic carbonyl optionally having substituents", "C_{6-14} aryl-carbamoyl optionally having substituents", "5- or 6-membered heterocyclic carbamoyl optionally having substituents" and "C_{6-14} arylsulfonyl optionally having substituents" is exemplified by those mentioned as the "substituent" in the above "C_{6-14} aryl optionally having substituents". The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The above-mentioned "acylamino" includes, for example, amino which is substituted by 1 or 2 of the above-mentioned "acyl" and preferably, acylamino represented by the formula: $-NR^5-COR^6$, $-NR^5-COOR^{6a}$, $-NR^5-SO_2R^{6a}$ or $-NR^5-CONR^{6a}R^{6b}$,

wherein, R^5 represents hydrogen atoms or C_{1-6} alkyl; R^6 has the same meanings as the above R^3; R^{6a} has the same meanings as the above R^{3a}; R^{6b} has the same meanings as the above R^4; etc.

For the "C_{1-6} alkyl" represented by R^5, those similar to the "C_{1-6} alkyl" represented by R^4 as mentioned above can be used.

Said "acylamino" is, preferably, formylamino, optionally

halogenated C_{1-6} alkyl-carboxamide, C_{6-14} aryl-carboxamide optionally having substituents (e.g., phenylcarboxamide, naphthylcarboxamide, etc.), optionally halogenated C_{1-6} alkoxy-carboxamide (e.g., methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), optionally halogenated C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), etc.

Furthermore, the "substituent" in the "C_{6-14} aryl-carboxamide optionally having substituents" is exemplified by those mentioned as the "substituent" in the above "C_{6-14} aryl optionally having substituents". The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

The above-mentioned "acyloxy" includes, for example, oxy which is substituted by one of the above-mentioned "acyl", and preferably, acyloxy represented by the formula: $-O-COR^7$, $-O-COOR^7$, $-O-CONHR^7$,

wherein, R^7 has the same meanings as the above-mentioned R^3; etc.

Said "acyloxy" is preferably, C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propanoyloxy, etc.), C_{6-14} aryl-carbonyloxy optionally having substituents (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy, etc.), optionally halogenated C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, trifluoromethoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g, methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g.,dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy optionally having substituents (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), nicotinoyloxy, etc.

Furthermore, the "substituent" in the "C_{6-14} aryl-carbonyloxy optionally having substituents" and "C_{6-14} aryl-carbamoyloxy

optionally having substituents" is exemplified by those mentioned as the "substituent" in the above "C_{6-14} aryl optionally having substituents". The number of the substituents is, for example, 1 to 5, preferably, 1 to 3. When the number of the substituents is 2 or more, these substituents may be the same or different.

Ar represents, preferably, "monocyclic aromatic group optionally having substituents" or "fused aromatic group optionally having substituents".

The "monocyclic aromatic group" in the "monocyclic aromatic group optionally having substituents" includes, preferably, phenyl, 2- or 3-thienyl, or 2-, 3- or 4-pyridyl.

Moreover, "fused aromatic group" in the "fused aromatic group optionally having substituents" includes, preferably, fused polycyclic aromatic heterocyclic group, more preferably, 2-benzothienyl, 2-benzofuranyl, indol-2-yl, and indol-3-yl.

The "substituent" in the "monocyclic aromatic group optionally having substituents" and "fused aromatic group optionally having substituents" includes, preferably, 1 or 2 substituents selected from halogen atoms, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy.

Ar is more preferably phenyl which may have 1 or 2 substituents selected from halogen atoms, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy.

Preferable examples of compound (I) include the following compounds:

1) a compound:

wherein either X or X' represents fluorine atoms and the other represents hydrogen atoms;

R^1 and R^2 each represent C_{1-6} alkyl (preferably, methyl);

Y represents a bond or C_{1-2} alkylene;

Q represents a bond, $-(CH_2)_{w1}CO(CH_2)_{w2}-$ or $-(CH_2)_{w3}COO(CH_2)_{w4}-$

(wherein the symbols have the same meanings as above);

T^1 represents CH, T^2 represents a nitrogen atom; and

Ar represents monocyclic aromatic group (preferably, phenyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl) or fused aromatic group (preferably, 2-benzothienyl, 2-benzofuranyl, indol-2-yl, indol-3-yl), each of which may have 1 or 2 substituents selected from halogen atoms, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy,

2) a compound:

wherein X represents chlorine atom, X' represents hydrogen atoms;

R^1 and R^2 each represent C_{1-6} alkyl (preferably, methyl);

Y represents C_{1-2} alkylene;

Q represents a bond, $-(CH_2)_{w1}CO(CH_2)_{w2}-$ or $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (wherein the symbols have the same meanings as above);

T^1 represents CH, T^2 represents a nitrogen atom; and

Ar represents monocyclic aromatic group (preferably, phenyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl) or fused aromatic group (preferably, 2-benzothienyl, 2-benzofuranyl, indol-2-yl, indol-3-yl), each of which may have 1 or 2 substituents selected from halogen atoms, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy,

3) a compound:

wherein X represents hydrogen atom, X' represents chlorine atom;

R^1 and R_2 each represents C_{1-6} alkyl (preferably, methyl);

Y represents a bond or C_{1-2} alkylene;

Q represents a bond, $-(CH_2)_{w1}CO(CH_2)_{w2}-$ or $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (wherein the symbols have the same meanings as above);

T^1 represents CH, T^2 represents a nitrogen atom; and

Ar represents monocyclic aromatic group (preferably, phenyl, 2- or 3-thienyl, 2-,3- or 4-pyridyl) or fused aromatic group (preferably, 2-benzothienyl, 2-benzofuranyl, indol-2-yl, indol-3-yl), each of which may have 1 or 2 substituents selected from halogen atoms, optionally halogenated C_{1-6} alkyl and optionally

halogenated C_{1-6} alkoxy.

As the salts of compound (I), for example, inorganic salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids can be mentioned. Preferable examples of inorganic salts include alkali metal salts such as sodium salt and potassium salt, etc; alkaline earth metal salts such as calcium salts, magnesium salts and barium salts, etc; aluminum salts, etc. Preferred salts with organic bases are exemplified by salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Preferred salts with inorganic acids are exemplified by salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Preferred salts with organic acids are exemplified by salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Preferred salts with basic amino acids are exemplified by salts with arginine, lysine, ornithine, etc. Preferred salts with acidic amino acids are exemplified by salts with aspartic acid, glutamic acid, etc.

Among these, pharmaceutically acceptable salts are preferable. Preferable examples include, when compound (I) has an acidic functional group, inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt, etc.) and ammonium salts, etc; and when compound (I) has a basic functional group, inorganic salts such as hydrochloride, sulfate, phosphate and hydrobromide, or, organic salts such as acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate and tartarate.

The prodrugs of compound (I) means a compound which is

converted into compound (I) through a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound which is enzymatically converted into compound (I) with oxidation, reduction, hydrolysis, etc.; a compound which is converted into compound (I) with gastric acid, etc.; etc. Examples of the prodrug of compound (I) include a compound wherein an amino group of compound (I) is substituted with acyl, alkyl, phosphoric acid, etc. (e.g., a compound wherein an amino group of compound (I) is substituted with eicosanoyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, tert-butyl, etc.); a compound wherein a hydroxy group of compound (I) is substituted with acyl, alkyl, phosphoric acid, boric acid, etc. (e.g., a compound wherein a hydroxy group of compound (I) is substituted with acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl, etc.); a compound wherein a carboxyl group of compound (I) is modified with ester, amide, etc. (e.g., a compound wherein a carboxyl group of compound (I) is modified with ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester, methyl amide, etc.); etc. These compounds can be produced by *per se* known methods from compound (I).

The prodrug of compound (I) may be a compound which is converted into compound (I) under the physiological conditions as described in "Pharmaceutical Research and Development", Vol. 7 (Drug Design), pages 163-198 published in 1990 by Hirokawa Publishing Co. (Tokyo, Japan).

Process for producing compound (I) is mentioned below.

Compound (I) can be produced by *per se* known means, for example, by the methods exemplified by the following schemes or

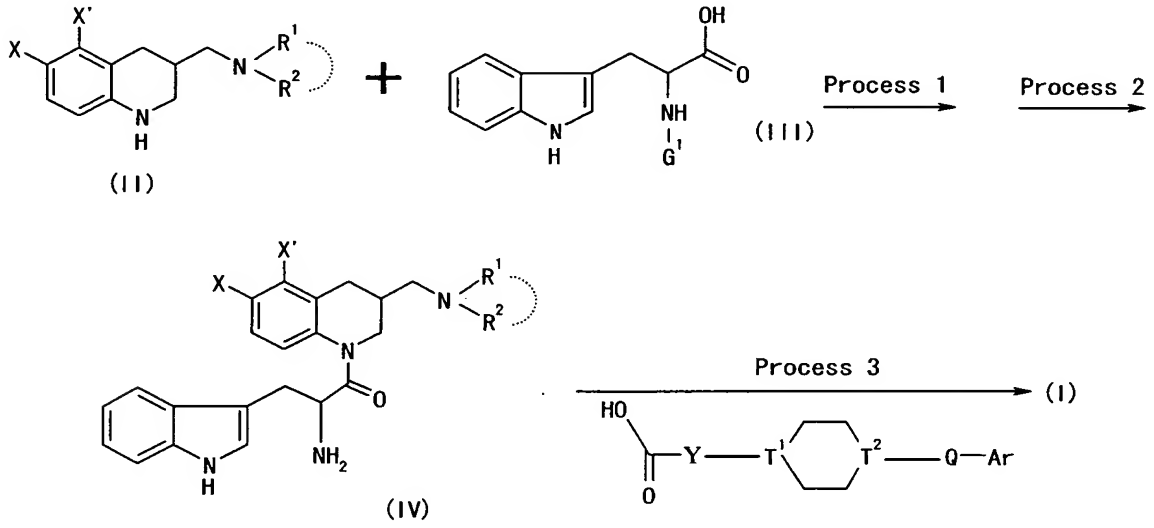
a similar method thereto, etc.

Compounds described in the following schemes may be in the form of salts. These salts are exemplified by those similar to the salts of compound (I).

"Room temperature" is normally meant to indicate a temperature falling between 0°C and 30°C in the present specification.

The following reaction such as alkylation, hydrolysis, amination, esterification, amidation, etherification, oxidation, reduction, urea reaction, etc. may be conducted according to *per se* known methods, for example, those described in Organic Functional Group Preparations, 2nd Ed., Academic Press Inc., 1989 and in Comprehensive Organic Transformations, VCH Publishers Inc., 1989. or a similar method thereto.

[scheme 1]



wherein, G^1 represents the protective group of amino group (e.g., 9-fluorenylmethoxycarbonyl, etc.) and the other symbols have the same meanings as above.

The protective group of amino group represented by G^1 includes the same protective group as those for amino group which will be later described. Among those, preferred is 9-fluorenylmethoxycarbonyl, etc.

Process 1: amidation

Said "amidation" includes, for example, the below mentioned method such as i) the method using a dehydrating/condensing agent, ii) the method in which carboxy is converted into the reactive derivative and then, condensed.

i) The method using a dehydrating/condensing agent

Compound (II), about 1 to about 5 equivalents of Compound (III), and about 1 to about 2 equivalents of a dehydrating/consensing agent are reacted in an inert solvent under room temperature for about 10 to 24 hours.

Said "dehydrating/condensing agent" includes, for example, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC), etc. Among those, WSC is preferred.

The "inert solvent" includes, for example, nitriles, amides, halogenated hydrocarbons, ethers, etc., which may be used as a mixture of two or more species. Among those, preferred is acetonitrile, DMF, dichloromethane, THF, etc.

In the present reaction, about one equivalent to about 1.5 equivalents of 1-hydroxybenzotriazole (HOBt) and/or about one equivalent to 5 equivalents of a base may be added if necessary.

Said base includes, for example;

1) strong bases such as alkali metal or alkaline earth metal hydrides (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride, etc.), alkali metal or alkaline earth metal amides (e.g., lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, etc.), alkali metal or alkaline earth metal lower-alkoxides (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), etc;

2) inorganic bases such as alkali metal or alkaline earth metal hydroxides (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, etc.), alkali metal or alkaline earth metal carbonates (e.g., sodium carbonate,

potassium carbonate, cesium carbonate, etc.), alkali metal or alkaline earth metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), etc.; and

3) organic bases such as amines exemplified by triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), etc., basic heterocyclic compounds exemplified by pyridine, imidazole, 2,6-lutidine, etc. Among these, preferred are triethylamine and 4-dimethylaminopyridine, etc.

ii) The method using the reactive derivative of carboxy

The reactive derivative of Compound (III) and about 1 to about 5 equivalents (preferably about 1 to about 3 equivalents) of Compound (II) are reacted in an inert solvent.

The reactive derivatives in the "reactive derivative of Compound (III)" include acid halide (e.g., acid chloride, acid bromide, etc.), mixed acid anhydride (e.g., anhydride with C_{1-6} alkyl carboxylic acid, C_{6-10} aryl carboxylic acid or C_{1-6} alkyl carbonic acid, etc.), active ester (e.g., ester with phenol optionally having substituents, 1-hydroxybenzotriazole or N-hydroxysuccinimide, etc.). The "substituent" in said "phenol optionally having substituents" includes, 1 to 5 of halogen atoms, nitro, optionally halogenated C_{1-6} alkyl or optionally halogenated C_{1-6} alkoxy. The concrete examples of "phenol optionally having substituents" are phenol, pentachlorophenol, pentafluorophenol, p-nitrophenol, etc. The reactive derivative is preferably acid halide.

The "inert solvent" includes, for example, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, water, etc., which may be used as a mixture of two or more species. Among these, preferred are tetrahydrofuran (THF), acetonitrile, dichloromethane, chloroform, etc.

The reaction temperature may be between about -20°C and

about 50°C, preferably at room temperature.

The reaction time falls between about 5 minutes and about 40 hours, preferably about 1 to about 5 hours.

In the present reaction, about 1 to about 10 equivalents, preferably about 1 to about 3 equivalents of a base is used if necessary.

As said "base", those exemplified in the above-mentioned "the method using a dehydrating/condensing agent" are used. Among them, preferred is sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, potassium hydrogen carbonate, triethylamine, pyridine, etc.

Process 2: deprotection

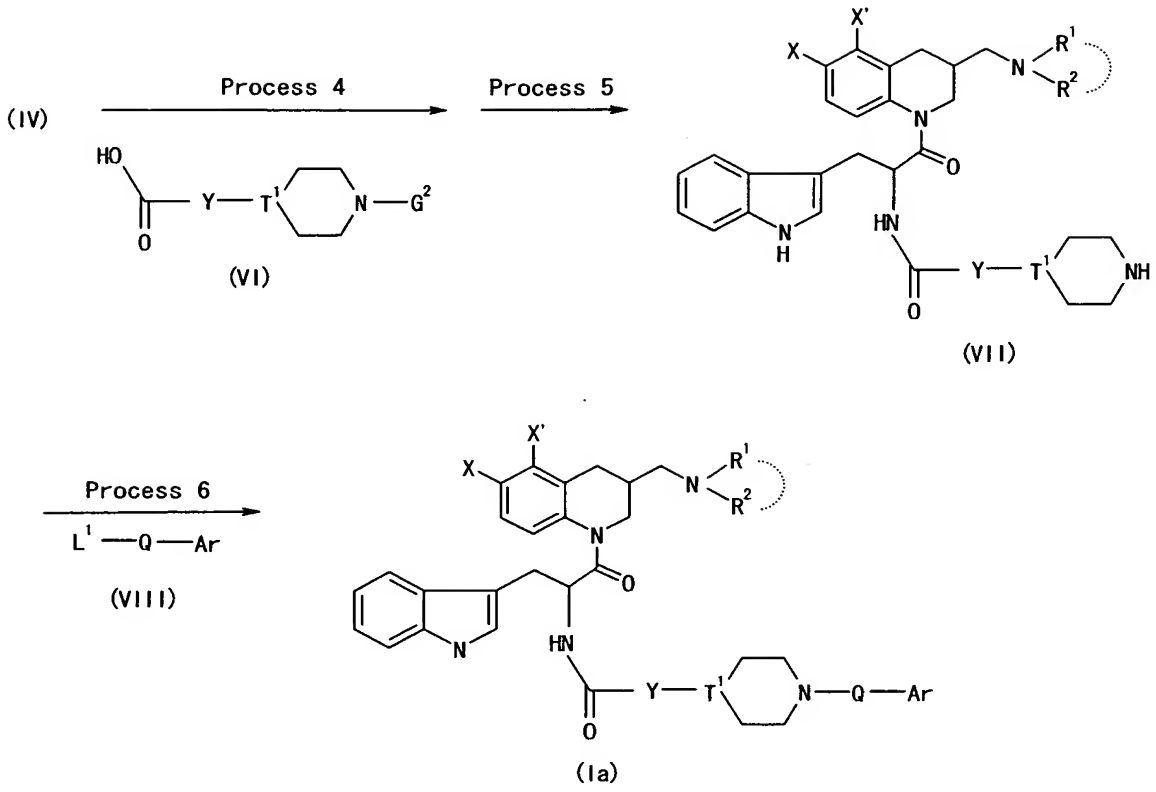
The present reaction is carried out by *per se* known method according to the kind of G^1 which is a protective group of amino group.

Process 3: amidation

Compound (I) can be produced according to amidation in the same manner as in Process 1 by reacting Compound (IV) and Compound (V).

Compound of the general formula (I) where T^2 is a nitrogen atom can be also produced according to the method represented by Scheme 2 and Scheme 3.

[Scheme 2]



wherein G^2 represents a protective group of an amino group (e.g., acetyl, trifluoroacetyl or benzyloxycarbonyl, etc.), L^1 represents a leaving group, the other symbols have the same meanings as above.

The "leaving group" represented by L^1 includes, for example, (1) halogen atoms (e.g., chlorine, bromine, iodine, etc.), (2) optionally halogenated C_{1-6} alkyl sulfonyloxy (e.g., methane sulfonyloxy, ethane sulfonyloxy, trifluoromethane sulfonyloxy, etc.), (3) C_{6-10} aryl sulfonyloxy optionally having substituents, (4) hydroxy, etc.

The substituent in said "C_{6-10} aryl sulfonyloxy optionally having substituents" includes, for example, 1 to 3 of halogen atoms, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, etc. The concrete examples of "C_{6-10} aryl sulfonyloxy optionally having substituents" are benzenesulfonyloxy, p-toluene sulfonyloxy, 1-naphthalene sulfonyloxy, 2-naphthalene sulfonyloxy, etc.

Process 4: amidation

According to the same amidation as in the above-mentioned Process 1, Compound (IV) and Compound (VI) are reacted.

Process 5: Deprotection

Compound (VII) can be produced by deprotecting the amide compound obtained in the above-mentioned Process 4. The present reaction can be carried out by *per se* known methods according to the kind of G^2 which is a protective group of amino group.

For example, when G^2 is trifluoroacetyl, the amide compound obtained in the above-mentioned process 4 is reacted with 1 to 20 equivalents (preferably 1 to 5 equivalents) of base in an inert solvent.

As said "base", those exemplified in the above-mentioned Process 1 are used. The base is, preferably potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, etc., more preferably, potassium carbonate.

The "inert solvent" includes, for example, alcohols, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, water, etc., which may be used as a mixture of two or more species. Among those, preferred are alcohols (e.g., methanol, ethanol, etc.), water or the mixture of these.

For example, when G^2 is benzyloxycarbonyl, catalytic reduction is conducted on the amide compound obtained in the above-mentioned Process 4.

Said catalytic reduction is carried out under the presence of a catalyst in an inert solvent under 1 to 100 torr (preferably 1 to 5 torr) of the hydrogen pressure.

The "catalyst" includes, for example, palladium catalysts (e.g., palladium-carbon, palladium-metal, etc.), platinum catalyst (e.g., platinum oxide, etc.), nickel catalysts (e.g, raney nickel, etc.), etc. Among those, preferred is palladium-carbon.

The amount of the catalyst used is generally about 0.01 to about 1 equivalent, preferably about 0.01 to about 0.5 equivalent of the amide compound.

The "inert solvent" includes, for example, alcohols, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, water, etc., which may be used as a mixture of two or more species. Among these, preferred is alcohols (e.g., methanol, ethanol, etc.), etc.

The reaction temperature may be between room temperature and 100°C, preferably at room temperature.

The reaction time falls between 0.1 hour and 24 hours, preferably 0.1 to 5 hours.

Process 6: Induction of the group represented by the formula -Q-Ar (wherein the symbols have the same meanings as above).

Compound (VII) and Compound (VIII) are reacted to obtain Compound (Ia). The present reaction can be carried out by *per se* known methods according to the kind of G^2 which is a protective group of amino group.

When a functional group adjacent to the leaving group L^1 is CO, SO or SO_2 at Q in Compound (VIII), the present reaction is conducted in the same manner as the amidation in the above-mentioned Process 1.

Moreover, when a functional group adjacent to the leaving group L^1 is non-carbonyl carbon atom at Q in Compound (VIII), the present reaction is conducted by alkylation.

Said alkylation is conducted by, for example, reacting Compound (VII) and about 1 to about 5 equivalents (preferably about 1 to about 2 equivalents) of compound (VIII) under the presence of base in an inert solvent.

As said "base", those exemplified in the above-mentioned Process 1 are used. Among those, preferred is potassium carbonate, sodium hydride, potassium hydroxide, etc.

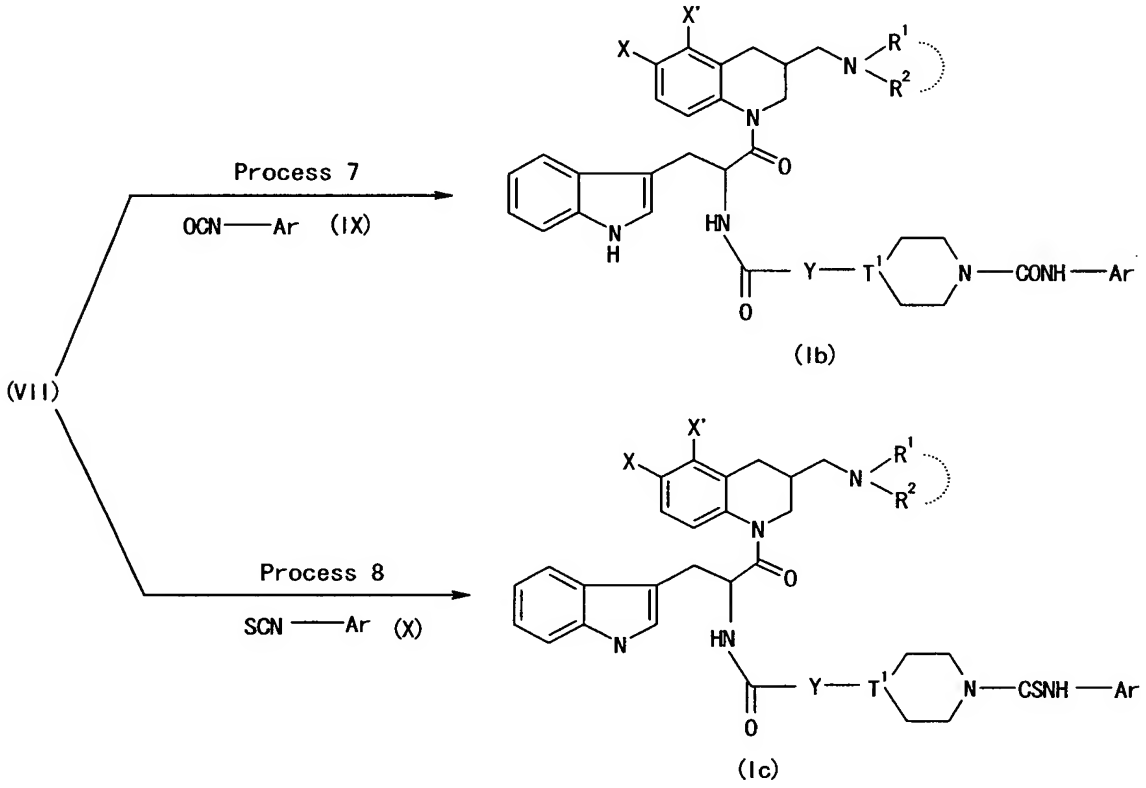
The "inert solvent" includes, for example, alcohols, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, water, etc., which may be used as a mixture of two or more species. Among these, preferred are acetonitrile,

N,N-dimethyl formamide (DMF), acetone, ethanol, pyridine, water, etc.

The reaction temperature may be between about -20°C and about 100°C, preferably between room temperature and 80°C.

The reaction time falls between 0.5 hour and 1 day.

[scheme 3]



wherein the symbols have the same meanings as above

Process 7: urea reaction

The compound where T^2 is a nitrogen atom and Q is -CONH- in the general formula (I), that is, Compound (Ib), can be produced by subjecting the Compound (VII) to urea reaction.

For said urea reaction, for example, Compound (VII) and 1 to 2 equivalents of Compound (IX) (e.g., phenylisocyanate, etc.) are reacted in an inert solvent.

The "inert solvent" includes, for example, ethers, halogenated hydrocarbons, aromatic solvents, nitriles, amides, ketones, sulfoxides, water, etc., which may be used as a mixture of two or more species. Among those, preferred are acetonitrile,

N,N-dimethylformamide (DMF), acetone, pyridine, water, etc.

The reaction temperature is between about -20°C and about 100°C, preferably between room temperature and 80°C.

The reaction time falls between 0.5 hour and 1 day.

The present reaction can be conducted under the presence of a base if necessary. Said "base" includes those exemplified in the above-mentioned Process 1. Among those, preferred are sodium hydride, potassium carbonate, carbonic acid, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, potassium hydrogen carbonate, triethylamine, pyridine, etc. The amount of the base used is, for example, catalyst amount to 2 equivalents of Compound (VII).

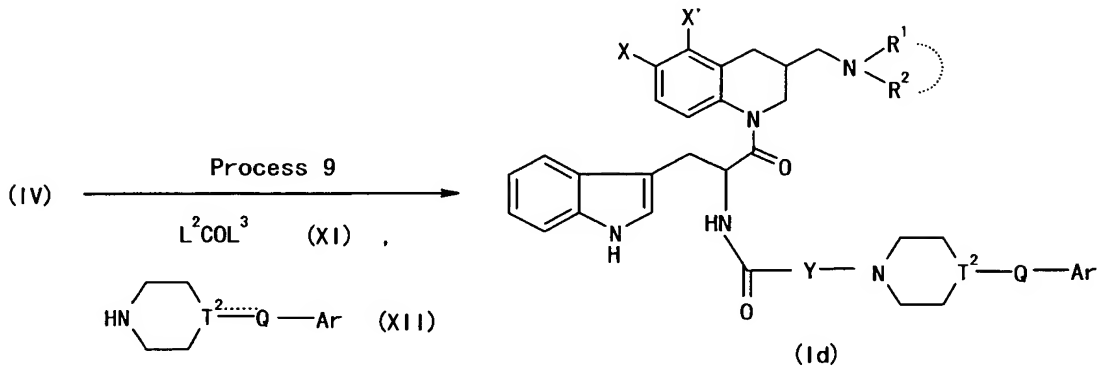
Process 8: thiourea reaction

The compound where T^2 is a nitrogen atom and Q is -CSNH- in the general formula (I), that is, Compound (Ic), can be produced by subjecting Compound (VII) to thiourea reaction.

For said thiourea reaction, for example, Compound (VII) and 1 to 2 equivalents of Compound (X) (e.g., phenylisothiocyanate, etc.) are reacted in an inert solvent. The present reaction is conducted in the same manner as in the above-mentioned urea reaction.

The compound where Y is a bond and T^1 is a nitrogen atom in the general formula (I), that is, Compound (Id), can be also produced according to Scheme 4.

[Scheme 4]



wherein L^2 and L^3 represent a leaving group; the other

symbols have the same meanings as above.

The leaving group represented by $L^2$and L^3 includes those exemplified as the above-mentioned L^1. Among those, preferred are chlorine or succinimideoxy and especially succinimideoxy is preferred.

Process 9: urea reaction

Compound (IV) and 1 to 2 equivalents of Compound (XI) are reacted in an inert solvent at room temperature for about 0.5 to 5 hours, and then 1 to 2 equivalents of Compound (XII) is reacted in an inert solvent at room temperature for about 0.5 to 24 hours.

The "inert solvent" includes, for example, nitriles, ethers, halogenated hydrocarbons, etc., which may be used as a mixture of two or more species. Among those, acetonitrile, THF, dichloromethane are preferred.

In the present reaction, about 1 to about 5 equivalents of a base (e.g., N-ethyldiisopropylamine, etc.) may be added if necessary.

In the thus obtained compound (I), intermolecular functional groups can be converted into the desired functional groups by combination of *per se* known chemical reactions. Examples of the chemical reactions include oxidation, reduction, alkylation, hydrolysis, amination, esterification, aryl-coupling reaction, deprotection, etc.

The above-mentioned "alcohols" includes, for example, methanol, ethanol, isopropanol, tert-butanol, etc.

The above-mentioned "ethers" includes, for example, diethyl ether, tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane, etc.

The above-mentioned "halogenated hydrocarbons" includes, for example, dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride, etc.

The above-mentioned "aromatic solvents" includes, for example, benzene, toluene, xylene, pyridine, etc.

The above-mentioned "amides" includes, for example, N,N-dimethylformamide (DMF), N,N-dimethylacetamide, N-methylpyrrolidone, etc.

The above-mentioned "ketones" includes, for example, acetone, methylethylketone, etc.

The above-mentioned "sulfoxides" includes for example, dimethylsulfoxide (DMSO), etc.

The above-mentioned "nitriles" includes, for example, acetonitrile, propionitrile, etc.

The above-mentioned "esters" includes, for example, ethyl acetate, etc.

In the above-mentioned reactions where the starting compounds are substituted by any of amino, carboxy, hydroxy or carbonyl, those groups may be protected by ordinary protective groups which are generally used in peptide chemistry, etc. The protective groups may be removed after the reaction, if necessary, to give the desired compounds.

The protective group of amino includes, for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g., benzylcarbonyl, etc.), C_{7-14} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, etc.), trithyl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g., 1-allyl, etc.), etc. These groups may be substituted by 1 to 3 of halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, etc.) or nitro, etc.

The protective group of carboxy includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C_{7-11} aralkyl (e.g., benzyl, etc.), phenyl, trithyl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-

butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g., 1-allyl, etc.), etc. These groups may be substituted by 1 to 3 of halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, etc.) or nitro, etc.

The protective group of hydroxy includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trithyl, C_{7-10} aralkyl (e.g., benzyl, etc.), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g., benzylcarbonyl, etc.), 2-tetrahydropyranyl, 2-tetrahydrofuranyl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g., 1-allyl, etc.), etc. These groups may be substituted by 1 to 3 of halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl (e.g., methyl, ethyl, propyl, etc.), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, etc.), or nitro, etc.

The protective group of carbonyl includes, for example, cyclic acetal (e.g., 1,3-dioxane, etc.), non-cyclic acetal (e.g., di-C_{1-6} alkylacetal, etc.), etc.

Those protective groups may be removed by *per se* known methods, for example, the methods described in Protective Groups in Organic Synthesis, published by John Wiley and Sons, 1980, etc. For example, employed are the methods using acids, bases, ultraviolet ray, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilylhalide (e.g., trimethylsilyliodide, trimethylsilylbromide, etc.), etc.; and reduction, etc.

Compound (I) can be isolated and purified by any known procedures, for example, through solvent extraction, pH adjustment, redistribution, crystallization, recrystallization, chromatography, etc. The starting compounds for compound (I) and their salts can be also isolated and purified according to the same known procedures as above, but without any isolation

procedure, they may be used in the next step while they are in reaction mixtures.

Compound (I) may also be in the form of hydrates or non-hydrates thereof.

Where compound (I) includes optical isomers, stereo isomers, regio isomers and rotational isomers, those are within the scope of compound (I), and can be isolated as their single compound through *per se* known synthesis or separation. For example, where optical isomers of compound (I) exist, those resolved from their mixtures through optical resolution are within the scope of compound (I).

The optical isomers can be produced by *per se* known methods. Concretely, optically active synthetic intermediates or mixtures of racemate of the final product are subjected to ordinary optical resolution to give the corresponding optical isomers.

For the optical resolution, employable are *per se* known methods, such as a fractional recrystallization method, a chiral column method, a diastereomer method, etc.

1) Fractional Recrystallization Method

The method which comprises allowing a racemate to react with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.) to give a salt, which is then isolated through fractional recrystallization method, followed by, when desired, subjecting the isolated compound to neutralization to obtain free optical isomers.

2) Chiral Column Method

The method of separating a racemate or a salt thereof, which comprises utilizing a column for fractionating optical isomers (chiral column). In the case of liquid column chromatography, for example, a mixture of optical isomers is applied to a chiral column, such as ENANTIO-OVM (manufactured by

Tosoh Corp.), CHIRAL SERIES (manufactured by Daicel Co.), etc., which is then eluted with water, various buffers (e.g., phosphate buffer) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.), singly or as a suitable mixture of them, to isolate the individual optical isomers. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Science Co.), etc. is used for isolation.

3) Diastereomer Method

A racemic mixture is chemically reacted with an optically-active reagent to give a mixture of diastereomer, which is subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to give single compounds. The thus-isolated single compounds are then chemically processed, for example, through hydrolysis to thereby remove the optically-active reagent site from the compounds to obtain optical isomers. For example, where compound (I) has a hydroxy group or a primary or secondary amino group in the molecule, it is condensed with an optically-active organic acid (e.g., MTPA [α-methoxy-α-(trifluoromethyl)phenyl-acetic acid], (-)-menthoxyacetic acid, etc.) or the like to give the corresponding ester-type or amide-type diastereomer. On the other hand, where compound (I) has a carboxylic acid group, it is condensed with an optically-active amine or alcohol reagent to give the corresponding amide-type or ester-type diastereomer. The thus-isolated diastereomer is then subjected to acidic or basic hydrolysis, through which it is converted into the optical isomer of the original compound.

Compound (I) has an optical active center at 2-position in 3-(indol-3-yl)propanoyl group. And in said optical active center, there exist (R)-isomer and (S)-isomer. Among those, preferred is (R)-isomer.

Compound (I) has an excellent somatostatin receptor binding inhibition activity (i.e., somatostatin receptor agonist

activity and antagonist activity). Especially compound (I) has a selective somatostatin subtype 2 receptor (SSTR2) binding inhibition activity. Among those, it has a somatostatin subtype 2 receptor agonist activity.

Compound (I) acts through various intracellular signal transduction systems with which somatostatin is associated. The "intracellular signal transduction systems" include, for example, that which involves adenylate cyclase, K^+ channels, Ca^{2+} channels, dephosphorylation of protein, phospholipase C/inositol trisphosphate production systems, MAP kinase, Na^+/H^+ exchanger, phospholipase A2, a transcription factor such as NF-κB. Compound (I) modulates a direct or indirect cell proliferation inhibitory action or apoptosis both of which are associated with somatostatin.

Further, compound (I) is low in its toxicity, and enhances or inhibits production and/or secretion of a variety of hormones, growth factors and physiologically active substances, etc. by effecting on somatostatin receptors in mammals (e.g., human, cattle, horse, dog, cat, monkey, mouse and rat, especially, human).

The "hormones" include, for example, growth hormone (GH), growth hormone-releasing hormones (GHRH), thyroid stimulating hormone (TSH), prolactin, insulin, glucagon, etc. The "growth factors" include, for example, insulin-like growth factor-1 (IGF-1) and vascular endothelial cell growth factor (VEGF). Said "physiologically active substances" include, for example, vasoactive intestinal polypeptide (VIP), gastrin, glucagon-like peptide-1, amylin, substance-P, CCK (cholecystokinin), amylase, interleukins such as interleukin-6 (IL-6), interleukin-1 (IL-1), etc., cytokines such as TNF-α, etc., cardiotropin, etc.

Therefore, compound (I) is safe, and useful for diseases associated with disorders of the above intracellular signal transduction systems (e.g., diseases accompanied by excess sthenia or suppression, etc.); disorders of regulating cell

proliferation; diseases accompanied by disorders of production and/or secretion of hormones, growth factors, physiologically active substances, etc.; or facilitating growth, immune, gastroenteric or metabolic functions, etc; and the like.

For example, compound (I) is useful (1) for drugs for treatment of tumors such as acromegaly, TSH-producing tumors, nonsecretory (afunctional) hypophysial tumors, ectopic ACTH (adrenocorticotrophic hormone)-producing tumors, medullar thyroid carcinoma, VIP-producing tumors, glucagon-producing tumors, gastrin-producing tumors, insulinoma and carotinoid, (2) for drugs for treatment of insulin-dependent and non-insulin dependent diabetes mellitus or a variety of diseases associated with them, namely diabetic complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, Doan syndrome and orthostatic hypotension, (3) for drugs for treatment of obesity or overeating, etc caused by improvement of hyperinsulinemia or inhibition of appetite, etc. (4) for drugs for treatment of acute pancreatitis, chronic pancreatitis, pancreal/intestinal fistula, hemorrhagic ulcer, peptic ulcer, gastritis, hyperchylia, regurgitant esophagitis, etc. (5) for drugs for improvement of various symptoms accompanied by the *Helicobacter pylori* infection, for example, inhibitors of gastrin hypersecretion, etc (6) for drugs for inhibition of amylase secretion accompanied by endoscopic cholangiopancreatography, and drugs for prognostic treatment of surgical operation of pancreas, (7) for drugs for treatment of diarrhea due to intestinal malabsorption, promotion of secretion or dyskinesia of the digestive tracts (for example, short bowel syndrome, etc.), diarrhea due to the drugs for cancer chemotherapy, diarrhea due to congenital small intestine atrophy, diarrhea due to neuroendocrine tumors such as VIP-producing tumors, diarrhea due to AIDS, diarrhea due to graft versus host reaction accompanied by bone marrow transplantation, diarrhea due to diabetes mellitus, diarrhea due to celiac plexus blocking,

diarrhea due to systemic sclerosis and diarrhea due to eosinophilia, etc. (8) for drugs for treatment of dumping syndrome, irritable colitis, Crohn disease and inflammatory bowel disease, etc. (9) for drugs for treatment of tumors or cancers (e.g., thyroid cancer, large bowel cancer, breast cancer, prostatic cancer, small cell lung cancer, non-small cell lung cancer, pancreatic cancer, stomach cancer, cholangiocarcinoma, hepatic cancer, vesical cancer, ovarian cancer, melanoma, osteosarcoma, chondrosarcoma, malignant pheochromocytoma, neuroblastoma, brain tumors, thymoma, renal cancers, etc.), leukemia (e.g., leukemia of basophilic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin disease, and non-Hodgkin lymphoma, etc.); the drugs can be used for monotherapy or concomitant therapy with other anticancer drugs such as Tamoxifen, LHRH agonists, LHRH antagonists, interferon-α, β and γ, interleukin-2, etc.), (10) for drugs for prevention or treatment of hypertrophic cardiomyopathy, arteriosclerosis, valvular disease, myocardiac infarction (especially, myocardiac infarction post percutaneous transluminal coronary arterioplasty) and reangioplasty, (11) for drugs for treatment of hemorrhage of esophageal varicosis, cirrhosis and peripheral blood vessel disorders, (12) for drugs for treatment of diseases accompanied by general or local inflammation, for example, polyarteritis, rheumatoid arthritis, psoriasis, sunburn, eczema and allergy (e.g., asthma, atopic dermatitis and allergic rhinitis, etc.), because they modulate the secretion of physiologically active substances acting on the immune system (e.g., Substance P, tachykinin and cytokines), (13) for drugs for treatment of dementia (e.g., Alzheimer's disease, Alzheimer-type senile dementia, vascular/multi-infarct dementia, etc.), schizophrenia, epilepsy, depression, generalized anxiety disorder, sleep disorder, and multiple sclerosis, because they give influence on the production or secretion of nerve regulators, (14) for drugs for treatment of oculopathy (e.g.,

glaucoma, etc.), (15) for drugs for prevention or treatment of acute bacterial meningitis, acute virus encephalitis, adult respiratory distress syndrome, bacterial pneumonia, severe systemic mycotic infection, tuberculosis, spinal damage, bone fracture, hepatic failure, pneumonia, alcoholic hepatitis, virus A hepatitis, virus B hepatitis, virus C hepatitis, AIDS infection, human papilloma virus infection, influenza infection, metastasis of cancer, multiple myeloma, osteomalacia, osteoporosis, bone Paget disease, nephritis, renal failure, sepsis, septic shock, hypercalcemia, hypercholesterolemia, hypertriglyceridemia, hyperlipemia, systemic lupus erythematosus, transient ischemic attack and alcoholic hepatitis, etc., (16) for cure of organ transplantation, burns, trauma, and alopecia, etc. (17) as analgesics to suppress or relieve chronic or acute pain (e.g., postoperative pain, inflammatory pain, dental pain, bone disease (e.g., arthritis, rheumatism, osteoporosis, etc.) derived pain), (18) for imaging of tumors having somatostatin receptors after introducing radioactive substance (e.g., ^{123}I, ^{125}I, ^{111}In, etc.) to compound (I) directly or via a suitable spacer, and (19) for targeting tumors having somatostatin receptors after introducing anti-cancer drugs to compound (I) directly or via a suitable spacer.

Somatostatin is associated with secretion of growth hormone (especially in the case of SSTR2), therefore, compound (I), when it is used directly or for the purpose of promoting secretion of growth hormone, can provide the same effect and use as growth hormone itself. Thus, compound (I) can be used for prevention or treatment of diseases or symptoms caused by insufficiency of growth hormone or IGF-1.

The "prevention or treatment of diseases or symptoms caused by insufficiency of growth hormone or IGF-1" includes, for example, treatment of insulin-dependent and non-insulin dependent diabetes mellitus or a variety of diseases associated with them, namely diabetic complications such as diabetic

retinopathy, diabetic nephropathy, diabetic neuropathy, Doan syndrome and orthostatic hypotension, etc.; prevention of adverse effects caused by disassimilation of glucocorticoid; prevention or treatment of osteoporosis; stimulation of immune system (e.g., promotion of increase in hemocytes such as lymphocyte; strengthening of an antimicrobial activity or an antiviral activity); promotion of cure of burns and trauma; acceleration in the treatment of bone fracture; treatment of acute or chronic renal diseases; treatment or improvement of diseases or symptoms (short stature, delayed growth) associated with insufficiency of growth hormone in adults or infants; treatment of obesity; promotion of recovery after surgical operations; improvement of delayed growth associated with Prader-Willi syndrome and Turner's syndrome; treatment of delayed intrauterine growth and skeletogenous disorders; treatment of peripheral neuropathy; treatment of Noonan's syndrome, schizophrenia and depression; treatment or prevention of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease; treatment of pulmonary insufficiency and ventilation dependence; treatment of malabsorption syndrome; improvement of cachexia or protein loss caused by cancer or AIDS; promotion of weight increase or proteopexis in patients in the case of TPN (total parenteral nutrition); treatment of hyperinsulinemia; promotion of induction of ovulation; improvement of menopausal disorders; improvement of senile constitution. Further, the compound of the present invention is useful in mammals such as domestic animals for promotion of growth; increase in milk production; strengthening of an antimicrobial or antiviral activity by stimulation of immune system; stimulation in growth of wool in sheep. When used for the above-mentioned purposes, for example, for the treatment of osteoporosis, the compound can be used along with other therapeutic agents for osteoporosis (e.g., bisphosphonates, vitamin D preparations, calcitonin preparations, PTH

preparations, Osten, etc.). In the case of diabetes and diseases associated therewith, the compound can be used along with other therapeutic agents for diabetes (e.g. thiazolidinedione drugs such as troglitazone, pioglitazone, rosiglitazone etc., glucagon antagonists, glucose absorption inhibitors such as acarbose). In addition, the compound can be used along with hormones promoting other growth hormone secretion (e.g., GHRH), GH or IGF-1. For amelioration of menopausal disorders, the compound can be used along with hormone substitution therapy (e.g., treatment method using estrogen agents, Raloxifene or Tamoxifen). For the purpose of promoting immune system, the compound can be used along with cytokines or cytokine activity enhancing agents.

A pharmaceutical composition of the invention can be produced according to a per se known method. Said pharmaceutical composition can be produced by mixing compound (I) and a pharmacologically acceptable carrier according to any *per se* known method.

The dosage forms of the pharmaceutical composition include, for example, tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories, sustained release preparations, etc. Compound (I) and the pharmaceutical composition of the present invention can be safely administered orally or parenterally (e.g., by local, rectal and intravenous administration, etc.).

The content of compound (I) in a pharmaceutical composition of the present invention is, for instance, 0.1 to 100 weight percent of the whole composition. The dose of the pharmaceutical composition can be appropriately selected depending on the subject of administration, route of administration, disease, etc. For instance, the dose per administration when a pharmaceutical composition of the invention is orally administered as an agent for treating

glaucoma to an adult patient (body weight: about 60 kg), is about 0.1 to about 500 mg, preferably about 1 to about 100 mg, more preferably about 5 to about 100 mg in terms of an effective ingredient (compound (I)). These amounts can be divided into one to several doses per day for administration.

Here, examples of the pharmacologically acceptable carriers used for production of a pharmaceutical composition of the present invention include various organic or inorganic carrier substances which are commonly used as materials for pharmaceutical preparations, such as excipients, lubricants, binders, and disintegrators in solid preparations; solvents, solubilizing agents, suspending agents, isotonizing agents, buffering agents, soothing agents, in liquid preparations. In addition, additives such as antiseptics, antioxidants, coloring agents, sweeteners, absorbents, moistening agents, can be used, if necessary.

Examples of the excipients include lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid, etc.

Examples of the lubricants include magnesium stearate, calcium stearate, talc, colloidal silica, etc.

Examples of the binders include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, saccharose, gelatin, methylcellulose, carboxymethylcellulose sodium, etc.

Examples of the disintegrators include starch, carboxymethylcellulose, carboxymethylcellulose calcium, crosscarmellose sodium, carboxymethylstarch sodium, L-hydroxypropylcellulose, etc.

Examples of the solvents include water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, etc.

Examples of the solubilizing agents include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol,

trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

Examples of the suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl amino propionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate, etc.; or hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

Examples of the isotonizing agents include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

Examples of the buffering agents include buffer solutions of phosphate, acetate, carbonate and citrate, etc.

Examples of the soothing agents include benzyl alcohol, etc.

Examples of the antiseptics include paraoxybenzoates, chlorobutanol, benzyl alcohol, phenethylalcohol, dehydroacetic acid, and sorbic acid, etc.

Examples of the antioxidants include sulfite, ascorbic acid, etc.

【Embodiment of the Invention】

The present invention will be explained in more detail by the following Reference Examples, Examples, Formulation Example and Experimental Examples. These are not intended to restrict the present invention, and may be modified within the range of not deviating the scope of this invention.

"Room temperature" in the following Reference Examples and Examples means a temperature of 0°C to 30°C. For drying an organic layer, anhydrous magnesium sulfate or anhydrous sodium sulfate was employed. Unless otherwise specifically indicated, "%" means percent by weight.

The IR absorption spectra were measured in a diffused reflection method using a Fourier transform infrared spectrophotometer.

The meanings of the abbreviations used in the present specification are as follows:

s: singlet

d: doublet

dd: double doublet

dt: double triplet

t: triplet

q: quartet

m: multiplet

br: broad

J: coupling constant

Hz: Hertz

$CDCl_3$: deuterated chloroform

DMSO-d_6: deuterated dimethylsulfoxide

THF: tetrahydrofuran

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxide

WSC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

^{1}H-NMR: proton nuclear magnetic resonance spectrum (generally measured as the free form of each sample in $CDCl_3$)

IR: infrared absorption spectrum

Me: methyl

Et: Ethyl

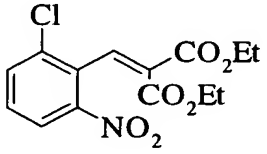
HOBt: 1-hydroxy-1H-benzotriazol

IPE: diisopropyl ether

【Example】

Reference Example 1

2-[(2-chloro-6-nitrophenyl)methylidene]malonic diethyl



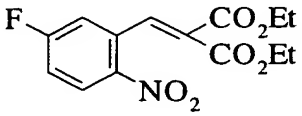
To a solution of 2-chloro-6-nitrobenzaldehyde(20.23 g) and

malonic diethyl (17.63 g) in acetic anhydride (36 ml) was added potassium hydrogen carbonate (16.48 g). The mixture was stirred at 110°C for two hours. After the reaction solution was cooled down, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine. After drying, the solution was concentrated. The residue was purified by silica gel column chromatography (developing solvent: ethyl acetate/hexane = 4/1) and gave the title compound (34.89 g).

^{1}H-NMR δ: 1.00(3H,t), 1.37(3H,t), 4.03(2H,q), 4.36(2H,q), 7.48(1H,dt), 7.71(1H,dd), 8.00(1H,s), 8.04(1H,dd).

Reference Example 2

2-[(5-fluoro-2-nitrophenyl)methylidene]malonic diethyl

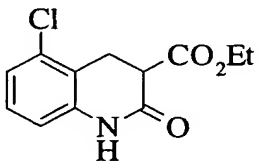


The title compound was obtained according to the same method as Reference Example 1.

^{1}H-NMR($CDCl_3$)δ: 1.10(3H,t), 1.36(3H,t), 4.15(2H,q), 4.35(2H,q), 7.10-7.30(2H,m), 8.13(1H,s), 8.28(1H,dd).

Reference Example 3

5-chloro-2-oxo-1,2,3,4-tetrahydro-3-quinoline carboxylic acid ethyl



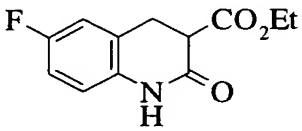
To a solution of 2-[(2-chloro-6-nitrophenyl)-methylidene]malonic diethyl (34.89 g) in ethanol (200 ml) was added sodium boron hydride (2.02 g) at 0°C . The mixture was stirred at 0°C for 30 minutes. Then, water was added to the mixture and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. To the residue in the aqueous solution of acetic acid (200 ml) was

added iron (25.7 g). The mixture was refluxed under heating for 90 minutes. Insoluble material was filtered off and the filtrate was concentrated. Water was added to the residue and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The obtained crude crystals were washed with IPE and the title compound (16.84 g) was obtained.

melting point: 174-176°C.

Reference Example 4

6-fluoro-2-oxo-1,2,3,4-tetrahydro-3-quinoline carboxylic acid ethyl

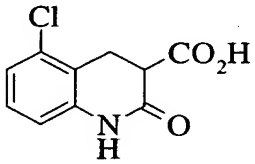


The title compound was obtained according to the same method as Reference Example 3.

melting point 166-168°C.

Reference Example 5

5-chloro-2-oxo-1,2,3,4-tetrahydro-3-quinoline carboxylic acid

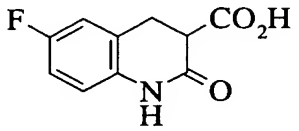


To a mixture of 5-chloro-2-oxo-1,2,3,4-tetrahydro-3-quinolinecarboxylic acid ethyl (15.23 g) in THF (180 ml) and methanol (120 ml) was dropwise added an aqueous solution of 1N sodium hydroxide (65 ml) at 0°C. The mixture was stirred at room temperature for 18 hours. To the reaction solution was dropwise added 1N hydrochloric acid (70 ml) at 0°C. Then, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. The obtained crude crystals were washed with IPE and the title compound (15.89 g) was obtained.

melting point: 179-186°C.

Reference Example 6

6-fluoro-2-oxo-1,2,3,4-tetrahydro-3-quinoline carboxylic acid

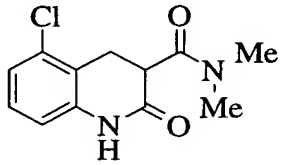


The title compound was obtained according to the same method as Reference Example 5.

melting point 144-147°C.

Reference Example 7

5-chloro-N,N-dimethyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinecarboxamide

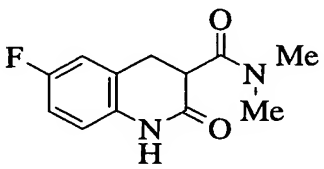


To a mixture of acetonitrile (100 ml) and THF (100 ml) was added 5-chloro-2-oxo-1,2,3,4-tetrahydro-3-quinolinecarboxylic acid (11.34 g), dimethylamine hydrochloride (4.95 g), HOBt (7.83 g), WSC (10.71 g) and triethylamine (17 ml). The reaction mixture was stirred at room temperature for 18 hours. To the reaction solution was added 10% of an aqueous solution of citric acid and extracted with ethyl acetate. The organic layer was washed with water, a saturated aqueous solution of sodium hydrogen carbonate and saturated brine, dried and concentrated. The residue was washed with IPE and the title compound (6.601 g) was obtained.

melting point: 257-261°C.

Reference Example 8

6-fluoro-N,N-dimethyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinecarboxamide

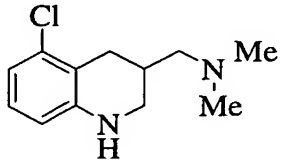


The title compound was obtained according to the same method as Reference Example 7.

melting point: 289-291°C. (decomposition)

Reference Example 9

5-chloro-3-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroquinoline

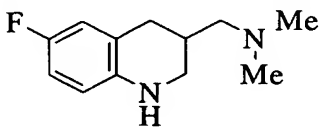


To a suspension of 5-chloro-N,N-dimethyl-2-oxo-1,2,3,4-tetrahydro-3-quinolinecarboxamide (5.059 g) in THF (180 ml) was added 1M borane-THF complex (80 ml). The reaction solution was refluxed under heating for 6 hours and left aside until it was cooled. The reaction solution was cooled down by ice, water (2 ml) and 6N hydrochloric acid (50 ml) was added thereto, stirred at room temperature for 15 hours and concentrated. The residue in methanol solution (50 ml) was refluxed under heating for 24 hours, to the residue was added an aqueous solution of 3N sodium hydroxide to make it as a base and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent: ethyl acetate/hexane = 1/10). The obtained crystals were washed with hexane and the title compound (3.52 g) was obtained.

melting point: 107-112°C.

Reference Example 10

3-(N,N-dimethylamino)methyl-6-fluoro-1,2,3,4-tetrahydroquinoline

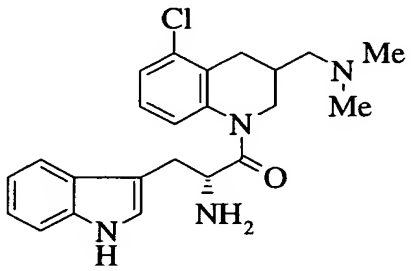


The title compound was obtained according to the same method as Reference Example 9.

melting point 104-105°C.

Reference Example 11

1-[2-(R)-amino-3-(indol-3-yl)propanoyl]-5-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroquinoline

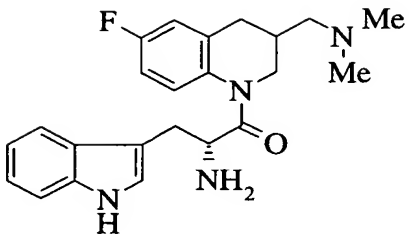


To a solution of N-(9-fluorenylmethoxycarbonyl)-D-triptophan (6.44 g) and DMF (0.14 ml) in THF (50 ml) was dropwise added oxalylchloride (1.6 ml) in THF (15 ml) solution at 0°C. The mixture was stirred at room temperature for 30 minutes. Then, to a mixture of a solution of 5-chloro-3-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroquinoline (1.13 g) in ethyl acetate (50 ml) and a saturated aqueous solution of sodium hydrogen carbonate (25 ml) was dropwise added the reaction solution at 0°C and stirred at room temperature for an hour, the organic layer was then separated. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent; ethyl acetate/hexane = 1:2 - 1:1) and concentrated. The residue was dissolved in methanol (60 ml), piperidine (2 ml) was added thereto and stirred for at room temperature for 12 hours. The reaction solution was concentrated and purified by alumina column chromatography (developing solvent; ethyl acetate/hexane = 1:2 - ethyl acetate/methanol = 20:1), the title compound was obtained as amorphous powders (0.828 g).

IR(KBr):3283, 2934, 2820, 2774, 1647, 1568, 1460, 1354, 1186, 741 cm^{-1}.

Reference Example 12

1-[2-(R)-amino-3-(indol-3-yl)propanoyl]-3-(R, S)-(N,N-dimethylamino)methyl-6-fluoro-1,2,3,4-tetrahydroquinoline



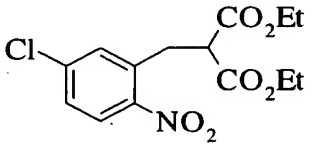
The title compound was obtained according to the same method as Reference Example 11.

IR(KBr):3289, 2928, 1644, 1497, 1456, 1244, 742 cm^{-1}.

MASS (APCIMASS), m/z 395[$(M+H)^+$].

Reference Example 13

2-(5-chloro-2-nitrobenzyl)malonic diethyl



To a mixture of 5-chloro-2-nitrobenzaldehyde (25 g), malonic diethyl (21.6 g) in acetic anhydride (50 ml) was added potassium hydrogen carbonate (11.9 g) and the mixture was stirred at 110°C for 45 minutes. The reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The crude product of 2-(5-chloro-2-nitrobenzylidene)malonic diethyl was obtained.

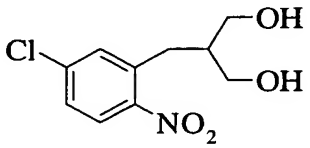
To a solution of a crude product of 2-(5-chloro-2-nitrobenzylidene) malonic diethyl in ethanol (250 ml) was added sodium boron hydride (3.3 g) under ice cooling and the solution was stirred for 30 minutes. Then, to the reaction solution was added 10% of an aqueous solution of citric acid. The solution was acidulated and concentrated. To the residue was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The residue was purified with silica gel column chromatography (developing solvent; hexane - hexane:ethyl acetate = 4:1) and the title compound (43 g) was obtained.

oily substance:

^{1}H-NMR ($CDCl_3$) δ: 1.23(6H, t), 3.49(2H, d), 3.84(1H, t), 4.19(4H, q), 7.10-7.46(2H, m), 7.99(1H, d).

Reference Example 14

2-(5-chloro-2-nitrobenzyl)-1,3-propanediol



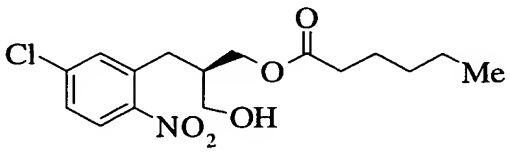
To a solution of a crude product of 2-(5-chloro-2-nitrobenzyl)malonic diethyl (30.0 g) in ethanol (300 ml) was added sodium boron hydride (10.3 g) under ice cooling. The mixture was stirred at room temperature for 12 hours. To the reaction solution was added 1N hydrochloric acid under ice cooling, stirred for 2 hours at room temperature and concentrated. The residue was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water and saturated brine, dried and concentrated. The residue was purified by silica gel column chromatography (developing solvent; hexane - ethyl acetate), the title compound (17 g) was obtained.

oily substance:

^{1}H-NMR ($CDCl_3$) δ: 1.90-2.20(1H, m), 2.80(2H, br s), 2.98(2H, d), 3.69(2H, dd), 3.85(2H, dd), 7.35(1H, dd), 7.43(1H, d), 7.92(1H, d).

Reference Example 15

2-(R)-(5-chloro-2-nitrobenzyl)-3-hydroxypropyl hexanoate



A mixture of 2-(5-chloro-2-nitrobenzyl)-1,3-propanediol (5.08 g), lipase PS-10527 (amano pharmaceuticals; 0.75 g), and vinyl hexanoate(10 ml) was shaked in IPE (500 ml) at 35°C for 21.5 hours. Enzyme was filtered off and the filtrate was concentrated. The residue was purified by silica gel

chromatography (developing solvent: hexane/ethyl acetate = 3/1), the title compound 6.64 g (99% ee) was obtained.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.91 (3H, t), 1.25-1.35 (4H, m), 1.63 (2H, m), 2.19 (1H, m), 2.33 (2H, t), 2.93 (1H, dd), 3.03 (1H, dd), 3.51 (1H, dd), 3.62 (1H, dd), 4.13-4.23 (2H, m), 7.36-7.40 (2H, m), 7.94 (1H, dd).

IR (KBr): 3450, 2957, 1734, 1525, 1343, 1175, 832 cm^{-1}.

$[\alpha]_D^{27}$=+24.6° (c=1.02, ethyl acetate).

Reference Example 16

2-(R)-(5-chloro-2-nitrobenzyl)-3-hydroxypropyl propionate

A mixture of 2-(5-chloro-2-nitrobenzyl)-1,3-propanediol (5.02 g), lipase PS-10527 (amano pharmaceuticals: 1.7 g), and vinyl propionate (20 ml) was shaked in diisopropyl ether (500 ml) at 35°C for 11 hours. High-performance chromatography analysis was performed on this reaction solution. According to the analysis, the yield of monoacyl body was 91%, the enantiomer excess was 98% ee. Enzyme was filtered off and the filtrate was concentrated to dryness to give the oily substance. This product was employed silica gel chromatography (silica gel 200 g, hexane/ethyl acetate = 3/1) and the title compound was obtained as a yellowish oily substance (4.21 g, 98% ee).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.16 (3H, t, J = 7.6 Hz), 1.68 (1H, br s,), 2.2 (2H, m), 2.37 (2H, q, J = 7.6 Hz), 2.94 (1H, dd, J = 7.1 and 13.4 Hz), 3.02 (1H, dd, J = 7.6 and 13.4 Hz), 3.51 (1H, dd, J = 5.7 and 11.5 Hz), 3.62 (1H, dd, J = 4.1 and 11.5 Hz), 4.16 (1H, dd, J = 6.1 and 11.5 Hz), 4.21 (1H, dd, J = 4.9 and 11.5 Hz), 7.39 (2H, m, Ph), 7.94 (1H, d, J = 8.5 Hz).

IR (KBr) 3452, 1735, 1525, 1344, 1196, 833 cm^{-1}.

$[\alpha]_D^{28}$=+7.35° (c=1.02, ethanol)

HPLC condition: column; CHIRALPAK AD (Daicel chemical industries)

mobile phase; n-hexane/2-propanol (925/75)

velocity; 0.8 ml/min

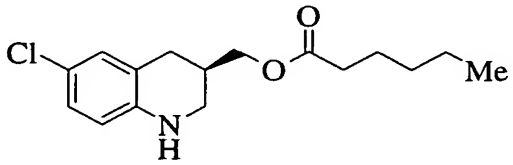
temperature; room temperature

detection; UV (225 nm)

retention time; 20, 24 min.

Reference Example 17

6-chloro-3-(R)-hexanoyloxymethyl-1,2,3,4-tetrahydroquinoline



To a solution of 2-(R)-(5-chloro-2-nitrobenzyl)-3-hydroxypropyl hexanoate (400 mg) in acetonitrile (8 ml) was added triethylamine (0.3 ml) under ice cooling. Then, methanesulfonyl chloride (0.11 ml) was added thereto and stirred for 15 minutes. To the reaction solution was added a saturated aqueous solution of sodium hydrogen carbonate under ice cooling and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated brine, dried and concentrated.

The crude product of 2-(S)-(5-chloro-2-nitrobenzyl)-3-[(methylsulfonyl)oxy]propyl hexanoate was obtained. The crude product of 2-(S)-(5-chloro-2-nitrobenzyl)-3-[(methylsulfonyl)oxy]propyl hexanoate was dissolved in THF (3 ml), acetic acid (1.5 ml)was added thereto under ice cooling. Then, zinc powders (760 mg) was added thereto under ice cooling and stirred under ice cooling for 30 minutes. The mixture was stirred at room temperature for two hours, zinc powders (760 mg) was added thereto and stirred for one hour. The reaction solution was filtered, the filtrate was concentrated under reduced pressure and the crude product of 2-(S)-(2-amino-5-chlorobenzyl)-3-[(methylsulfonyl)oxy]propyl hexanoate was obtained.

The crude product of 2-(S)-(2-amino-5-chlorobenzyl)-3-[(methylsulfonyl)oxy]propyl hexanoate was dissolved in THF (8 ml) and diisopropylethylamine (1 ml) was added thereto, stirred at 60°C for 12 hours under argon stream. To the reaction

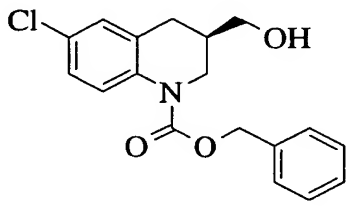
solution was added a saturated aqueous solution of sodium hydrogen carbonate and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried, concentrated. The residue was purified with alumina column chromatography (developing solvent; hexane - hexane:ethyl acetate = 10:1) and the title compound (234 mg) was obtained.

oily substance:

$[\alpha]_D^{20}$ = -25.1° (c = 0.505, methanol).

Reference Example 18

1-benzyloxycarbonyl-6-chloro-3-(R)-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline



To a solution of 6-chloro-3-(R)-hexanoyloxymethyl-1,2,3,4-tetrahydroquinoline (3.86 g) in pyridine (20 ml) was dropwise added benzyl chloroformate (3.0 ml). After stirring at room temperature for 30 minutes, water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water, a saturated aqueous solution of sodium hydrogen carbonate, water, saturated brine, dried and concentrated. The crude product of 1-benzyloxycarbonyl-6-chloro-3-(R)-hexanoyloxymethyl-1,2,3,4-tetrahydroquinoline was obtained.

The crude product of 1-benzyloxycarbonyl-6-chloro-3-(R)-hexanoyloxymethyl-1,2,3,4-tetrahydroquinoline was dissolved in a mixture of methanol (40 ml) and THF (40 ml) and an aqueous solution of 1N sodium hydroxide (20 ml) was added under ice cooling. The mixture was stirred at room temperature for 30 minutes, water was added to the reaction solution and concentrated. The residue was extracted with ethyl acetate.

The organic layer was washed with water and saturated brine, dried and then concentrated. The residue was purified by silica gel column chromatography (developing solvent; hexane - hexane:ethyl acetate = 2:1), the title compound (4.30 g) was obtained.

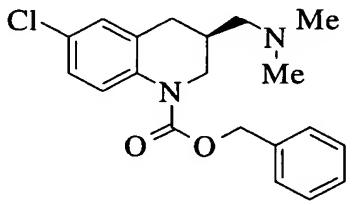
oily substance:

^{1}H-NMR ($CDCl_3$) δ: 1.95(1H, br s), 2.12-2.34(1H, m), 2.50(1H, dd), 2.89(1H, dd), 3.40-3.70(2H, m), 3.71(1H, dd), 3.85(1H, dd), 5.20(1H, d), 5.27(1H, d), 7.04-7.20(2H, m), 7.24-7.52(5H, m), 7.61(1H, d).

$[\alpha]_D^{20}$ = -19.3° (c = 0.502, methanol).

Reference Example 19

1-benzyloxycarbonyl-6-chloro-3-(S)-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline



To a solution of 1-benzyloxycarbonyl-6-chloro-3-(R)-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (4.20 g) in acetonitrile (84 ml) was added triethylamine (3 ml) under ice cooling. Methanesulfonyl chloride (1.2 ml) was added thereto and stirred for 15 minutes. To the reaction solution was added a saturated aqueous solution of sodium hydrogen carbonate and water under ice cooling and the solution was extracted with ethyl acetate. The organic layer was washed water and saturated brine, dried and concentrated. The crude product of 1-benzyloxycarbonyl-6-chloro-3-(R)-[[(methylsulfonyl)oxy]methyl]-1,2,3,4-tetrahydroquinoline was obtained.

The crude product of 1-benzyloxycarbonyl-6-chloro-3-(R)-[[(methylsulfonyl)oxy]methyl]-1,2,3,4-tetrahydroquinoline was dissolved in DMSO (50 ml), an aqueous solution of 50% dimethylamine (25 ml) was added thereto and the solution was

stirred at room temperature for 36 hours. To the reaction solution was added an aqueous solution of 5% potassium carbonate and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent; hexane - hexane:ethyl acetate = 10:1) the title compound (4.09 g) was obtained.

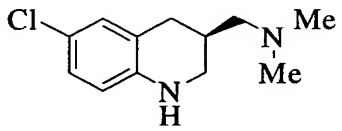
oily substance:

^{1}H-NMR ($CDCl_3$) δ: 2.0-2.4(3H, m), 2.20(6H, s), 2.46(1H, dd), 2.87(1H, dd), 3.25(1H, dd), 4.04-4.20(1H, m), 5.20(1H, d), 5.27(1H, d), 7.04-7.20(2H, m), 7.24-7.52(5H, m), 7.68(1H, d).

$[\alpha]_D^{20}$ = -26.0° (c = 0.503, methanol).

Reference Example 20

6-chloro-3-(R)-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline



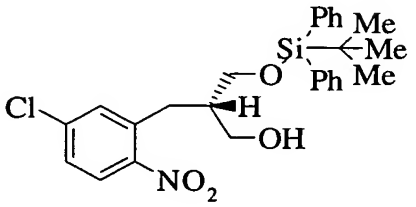
1-benzyloxycarbonyl-6-chloro-3-(S)-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline (3.89 g)was dissolved in 48% hydrobromic acid (20 ml) and the solution was stirred at room temperature for 18 hours. The reaction solution was diluted with water and the solution was extracted with hexane. To the aqueous layer was added an aqueous solution of 8N sodium hydroxide to adjust pH to 5. Then, potassium carbonate was added thereto to make the solution to become basic and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The residue was purified by re-crystallizing (hexane-ethyl acetate) and the title compound (1.47 g) was obtained.

melting point: 112-114°C

$[\alpha]_D^{20}$ = -46.7° (c = 0.503, methanol).

Reference Example 21

3-[[tert-butyl(diphenyl)silyl]oxy]-2-(S)-(5-chloro-2-nitrobenzyl)-1-propanol



To a solution of 2-(R)-(5-chloro-2-nitrobenzyl)-3-hydroxypropyl propionate (4.21 g) in DMF (20 ml) was added imidazole (2.0 g) and tert-butylchlorodiphenylsilane(4.0 ml) successively under ice cooling. The mixture was stirred at room temperature for 30 minutes. Then, water was added thereto and the reaction solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The crude product of 3-[[tert-butyl(diphenyl)silyl]oxy]-2-(S)-(5-chloro-2-nitrobenzyl)propyl propionate was obtained.

To the solution of the crude product of 3-[[tert-butyl(diphenyl)silyl]oxy]-2-(S)-(5-chloro-2-nitrobenzyl)propyl propionate in methanol (40 ml) was added potassium carbonate (2.0 g) and stirred for 4 hours. Water was added to the reaction solution and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried, and concentrated. The residue was purified by silica gel column chromatography (developing solvent; hexane - hexane:ethyl acetate = 5:1) and the title compound (6.15 g) was obtained.

oily substance:

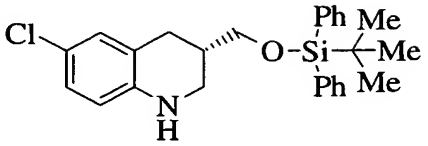
^{1}H-NMR ($CDCl_3$) δ: 1.09(9H, s), 1.94-2.16(1H, m), 2.09(1H, t), 2.90(1H, dd), 3.03(1H, dd), 3.60-3.88(4H, m), 7.26-7.56(8H, m), 7.62-7.74(4H, m), 7.89(1H, d).

$[\alpha]_D^{20}$ = +1.2° (c = 0.376, methanol).

Reference Example 22

3-(S)-[[[tert-butyl(diphenyl)silyl]oxy]methyl]-6-chloro-1,2,3,4-

tetrahydroquinoline



To a solution of 3-[[tert-butyl(diphenyl)silyl]oxy]-2-(S)-(5-chloro-2-nitrobenzyl)-1-propanol (6.00 g) in acetonitrile (120 ml) was added triethylamine (3.0 ml) and methanesulfonyl chloride (1.2 ml) successively under ice cooling. The mixture was stirred for 15 minutes, a saturated aqueous solution of sodium hydrogen carbonate was added thereto under ice cooling and water was also added thereto. The solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The crude product of 3-[[tert-butyl(diphenyl)silyl]oxy]-2-(R)-(5-chloro-2-nitrobenzyl)propyl methanesulfonate was obtained.

To the crude product of 3-[[tert-butyl(diphenyl)silyl]oxy]-2-(R)-(5-chloro-2-nitrobenzyl)propyl methanesulfonate in THF (60 ml) was added acetic acid (60 ml) and zinc powders(12.2 g) successively under ice cooling. The mixture was stirred for 15 minutes under ice cooling. Moreover, the solution was stirred at room temperature for 30 minutes. Zinc powders (8.1 g) was added to the reaction solution and stirred for 30 minutes. The reaction solution was filtered, the filtrate was concentrated under reduced pressure and the crude product of 2-(R)-(2-amino-5-chlorobenzyl)-3-[[tert-butyl(diphenyl)silyl]oxy]propyl methanesulfonate was obtained.

To the crude product of 2-(R)-(2-amino-5-chlorobenzyl)-3-[[tert-butyl(diphenyl)silyl]oxy]propyl methanesulfonate was added THF (80 ml) and diisopropylethylamine (10 ml). The mixture was stirred at 60°C for 10 hours under argon stream. An aqueous solution of saturated sodium hydrogen carbonate was added to the reaction solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The residue was purified silica gel

column chromatography (developing solvent; hexane - hexane:ethyl acetate = 10:1) and the title compound (5.14 g) was obtained.

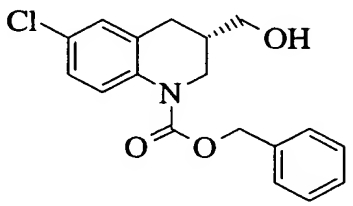
oily substance:

^{1}H-NMR ($CDCl_3$) δ: 1.06(9H, s), 1.34-1.80(1H, m), 2.08-2.32(1H, m), 2.50(1H, dd), 2.71(1H, dd), 3.07(1H, dd), 3.34-3.50(1H, m), 3.52-3.76(2H, m), 6.30-6.42(1H, m), 7.84-7.96(2H, m), 7.20-7.80(10H, m).

$[\alpha]_D^{20}$ = +13.3° (c = 0.433, methanol).

Reference Example 23

1-benzyloxycarbonyl-6-chloro-3-(S)-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline



To a solution of 3-(S)-[[[tert-butyl(diphenyl)silyl]-oxy]methyl]-6-chloro-1,2,3,4-tetrahydroquinoline (4.63 g) in ethyl acetate (50 ml) was added an aqueous solution (50 ml) of potassium carbonate (7.3 g). To the reaction solution was dropwise added benzyl chloroformate (3.0 ml) for 15 minutes under ice cooling. Then, the reaction solution was stirred at room temperature for 30 minutes. Water was added to the reaction solution and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The crude product of 1-benzyloxycarbonyl-3-(S)-[[[tert-butyl(diphenyl)silyl]oxy]methyl]-6-chloro-1,2,3,4-tetrahydroquinoline was obtained.

To the solution of the crude product of 1-benzyloxycarbonyl-3-(S)-[[[tert-butyl(diphenyl)silyl]-oxy]methyl]-6-chloro-1,2,3,4-tetrahydroquinoline in THF (60 ml) was added a solution of tetra-n-butylammonium fluoride in THF (1 M, 30 ml) under ice cooling. The mixture was stirred at room

temperature for 6 hours, water was added thereto and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The residue was purified by silica gel column chromatography (developing solvent; hexane - ethyl acetate) and the title compound (3.40 g) was obtained.

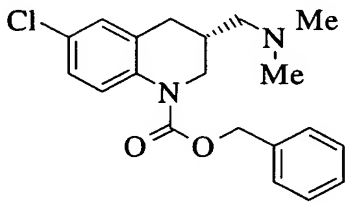
oily substance:

^{1}H-NMR ($CDCl_3$) δ: 1.95(1H, br s), 2.12-2.34(1H, m), 2.50(1H, dd), 2.89(1H, dd), 3.40-3.70(2H, m), 3.71(1H, dd), 3.85(1H, dd), 5.20(1H, d), 5.27(1H, d), 7.04-7.20(2H, m), 7.24-7.52(5H, m), 7.61(1H, d).

$[\alpha]_D^{20}$ = +20.3° (c = 0.381, methanol).

Reference Example 24

1-benzyloxycarbonyl-6-chloro-3-(R)-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline



To the solution of 1-benzyloxycarbonyl-6-chloro-3-(S)-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (3.3 g) in acetonitrile (66 ml) was added triethylamine (3 ml) and methanesulfonyl chloride (1.0 ml) successively under ice cooling. After stirring for 15 minutes, to the reaction solution was added a saturated aqueous solution of sodium hydrogen carbonate under ice cooling. Furthermore, water was added thereto, the reaction solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The crude product of 1-benzyloxycarbonyl-6-chloro-3-(S)-[[(methylsulfonyl)oxy]methyl]-1,2,3,4-tetrahydroquinoline was obtained.

To the mixture of the crude product of 1-benzyloxycarbonyl-6-chloro-3-(S)-[[(methylsulfonyl)oxy]methyl]-1,2,3,4-

tetrahydroquinoline in DMSO (40 ml) was added an aqueous solution of 50% dimethylamine (20 ml). The mixture was stirred at room temperature for 48 hours. An aqueous solution of sodium hydrogen carbonate and water was added to the reaction solution and the solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent; hexane - hexane:ethyl acetate = 10:1) and the title compound (3.3 g) was obtained.

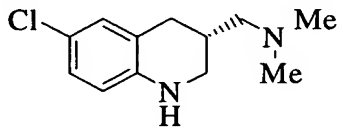
oily substance:

^{1}H-NMR ($CDCl_3$) δ: 2.0-2.4(3H, m), 2.20(6H, s), 2.46(1H, dd), 2.87(1H, dd), 3.25(1H, dd), 4.04-4.20(1H, m), 5.20(1H, d), 5.27(1H, d), 7.04-7.20(2H, m), 7.24-7.52(5H, m), 7.68(1H, d).

$[\alpha]_D^{20}$ = +30.5° (c = 0.158, methanol).

Reference Example 25

6-chloro-3-(S)-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline



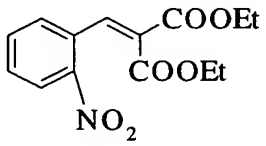
1-benzyloxycarbonyl-6-chloro-3-(R)-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline (3.2 g) was dissolved in 48% hydrobromic acid (16 ml) and the mixture was stirred at room temperature for 24 hours. The reaction solution was diluted with water and extracted with hexane. To the aqueous layer was added an aqueous solution of 8N sodium hydroxide to adjust its pH to approximately pH 5. Then, potassium carbonate was added thereto to make the solution to become basic. The solution was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried and concentrated. The precipitate crystals were washed with hexane and the title compound (1.85 g) was obtained.

melting point: 110-114°C

$[\alpha]_D^{20}$ = +46.7° (c = 0.502, methanol).

Reference Example 26

2-[(2-nitrophenyl)methylidene]malonic diethyl



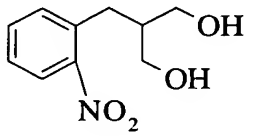
By azeotropic distillation, water was removed from a mixture of 2-nitrobenzaldehyde (10.0 g), malonic diethyl (15 ml), piperidine (1.3 ml) in benzene (90 ml) and while the distillation, the mixture was refluxed under heating for 25 hours. The reaction solution was concentrated and the residue was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 4/1) and the title compound (7.16 g) was obtained.

^{1}H-NMR (DMSO-d_6) δ: 1.03 (3H, t), 1.36 (3H, t), 4.08 (2H, q), 4.34 (2H, q), 7.43 (1H, d), 7.64 (1H, dt), 7.57 (1H, dt), 8.19(1H, s), 8.21 (1H, dd).

IR (KBr): 1731, 1721, 1526, 1344, 1260, 1214, 1203 cm^{-1}.

Reference Example 27

2-(2-nitrobenzyl)-1,3-propanediol



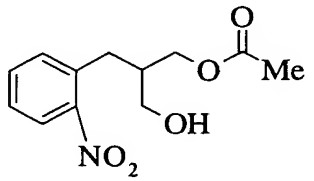
2-[(2-Nitrophenyl)methylidene]malonic diethyl (7.16 g) was dissolved in methanol (25 ml), sodium boron hydride (0.929 g) was added thereto and stirred at room temperature for 1.5 hours. To the reaction solution was added 1 N hydrochloric acid and the mixture was concentrated. The residue was dissolved in ethyl acetate and the solution was washed with water and saturated brine, dried and concentrated. The residue was dissolved in 0.1M phosphate buffer (pH 7.0) 30 ml and tetrahydrofuran 30 ml. To the reaction solution was added sodium boron hydride (4.59 g) and the solution was stirred at room temperature for 4.5 hours. Then, to the reaction solution was added saturated ammonium chloride, acetic acid and 1N

hydrochloric acid successively and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 1/5) and the title compound (1.45 g) was obtained.

melting point: 103-104°C (re-crystallized solvent: hexane/ethyl acetate).

Reference Example 28

3-hydroxy-2-(2-nitrobenzyl)propyl acetate



The mixture of 2-(2-nitrobenzyl)-1,3-propanediol (1.02 g), lipase P (amano pharmaceuticals; 1.0 g), vinyl acetate (1.0 ml) was shaked in IPE (300 ml) at 35°C for 5.5 hours. High-performance chromatography analysis was performed on the reaction solution. According to the analysis, the yield of monoacyl body is 92%, the enantiomer excess is 90% ee.

HPLC condition: column; CHIRALPAK AD (Daicel chemical industries)

mobile phase; hexane/2-propanol (925/75)

velocity; 0.8 ml/min

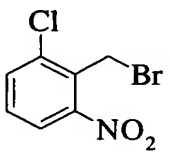
temperature; room temperature

detection; UV (224 nm)

retention time; 22, 27 min.

Reference Example 29

2-(bromomethyl)-1-chloro-3-nitrobenzene



To a solution of 2-chloro-6-nitrobenzaldehyde (25 g) in methanol (600 ml) was added sodium boron hydride (5.1 g) at 0°C

and the solution was stirred at the same temperature for 30 minutes. Then, diluted hydrochloric acid was gradually poured into the reaction solution. The mixture was stirred at room temperature and concentrated. To the residue was added ethyl acetate and water to perform separating extraction. The organic layer was washed with saturated brine, dried, concentrated. The residue was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 3/1). The obtained crystals were washed with ice-cooled hexane and (2-chloro-6-nitrophenyl)methanol (23.0 g) was obtained.

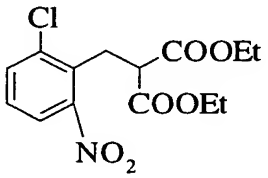
Under nitrogen stream, to 2-chloro-6-nitrophenylmethanol (22 g) was added 48% hydrobromic acid (250 ml) and the mixture was stirred at 90°C for 30 minutes. The reaction solution was extracted with IPE. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 6/1). The obtained solid was washed with hexane and the title compound was obtained (27.2 g).

^{1}H-NMR ($CDCl_3$) δ: 4.88 (2H, s), 7.44 (1H, t), 7.70 (1H, d), 7.87 (1H, d).

IR (KBr): 1523, 1351 cm^{-1}.

Reference Example 30

2-(2-chloro-6-nitrobenzyl)malonic diethyl



To a solution of malonic diethyl (19.3 ml) in dimethoxyethane (400 ml) was added sodium hydride (oiliness 60%, 5.1 g) at 0°C and added a mixture of 2-(bromomethyl)-1-chloro-3-nitrobenzene (26.5 g) in dimethoxyethane (100 ml) at 0°C successively. The solution was stirred at the same temperature for 30 minutes. Then, cold water was added to the reaction solution, stirred and concentrated. To the residue was added

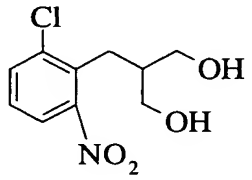
water and ethyl acetate to perform separating extraction. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 5/1) and the title compound (35.7 g) was obtained.

^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, t), 3.67 (2H, d), 3.81 (1H, t), 4.17 (4H, q), 7.36 (1H, t), 7.63 (1H, d), 7.76 (1H, d).

IR (neat): 1733, 1534 cm^{-1}.

Reference Example 31

2-(2-chloro-6-nitrobenzyl)-1,3-propanediol



To a solution of 2-(2-chloro-6-nitrobenzyl)malonic diethyl (35 g) in diethylether (275 ml)was added methanol (11.5 ml). To the reaction solution was added lithium boron hydride (6.0 g) at room temperature. The reaction solution was gradually poured into cold diluted hydrochloric acid and the solution was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. The obtained crude product was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 2/2.5 - 1/1.5) and the title compound (15.9 g) was obtained.

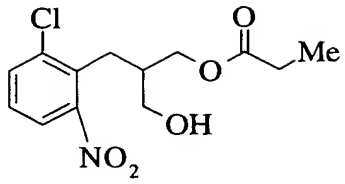
amorphous powders:

^{1}H-NMR ($CDCl_3$) δ: 2.05-2.20 (1H, m), 2.25 (2H, br s), 3.10 (2H, d), 3.09-3.80 (4H, m), 7.33 (1H, t), 7.63 (1H, d), 7.69 (1H, d).

IR (KBr): 3508, 3431, 1526, 1359 cm^{-1}.

Reference Example 32

(+)-2-(2-chloro-6-nitrobenzyl)-3-hydroxypropyl-1-propionate



A mixture of 2-(2-chloro-6-nitrobenzyl)-1,3-propanediol (11.02 g), MEITO Lipase AL (Meito Industries; 0.3 g), vinyl propionate (50 ml) was shaked in IPE (1000 ml) at 35°C for 24 hours. High-performance chromatography analysis was performed on the reaction solution. According to the analysis, the yield of monoacyl body was 90% and the enantiomer excess was 98% ee. Enzyme was filtered off and the filtrate was concentrated. The residue was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 3/1) and 12.59 g (93%, 96% ee) of the title compound was obtained.

^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t), 1.8 (1H, br s), 2.28 (1H, m), 2.34 (2H, q), 3.14 (2H, d), 3.55 (1H, dd), 3.61 (1H, dd), 4.11 (1H, m), 4.21 (1H, dd), 7.34 (1H, t), 7.63 (1H, t), 7.69 (1H, t).

IR (KBr): 3456, 1736, 1531, 1358, 1193, 801 cm^{-1}.

$[\alpha]_D^{28}$=+13.3° (c=1.11,ethanol)

HPLC condition: column; CHIRALPAK AD (Daicel chemical industries)

mobile phase; hexane/2-propanol (950/50)

velocity; 0.5 ml/min

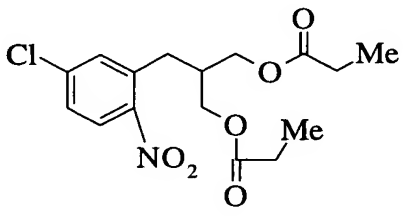
temperature; room temperature

detection; UV (225 nm)

retention time; 51, 56 min.

Reference Example 33

2-(5-chloro-2-nitrobenzyl)-1,3-propanediol bispropionate

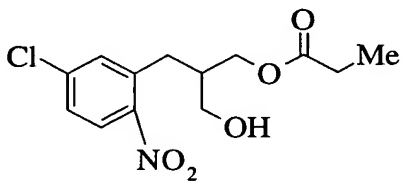


To a solution of 2-(5-chloro-2-nitrobenzyl)-1,3-propanediol (150 mg) in THF (5.0 ml) was added propionyl chloride (0.212 ml) and triethylamine (0.344 ml) successively. The mixture was stirred at room temperature for 5 hours. Then, the reaction solution was concentrated and IPE was added thereto. The organic layer was washed with water, saturated brine, dried and concentrated. The residue was purified by silica gel chromatography (developing solvent: hexane/ethyl acetate = 4/1) and the title compound (219 mg) was obtained.

IR (KBr): 1740, 1526, 1346, 1180, 835 cm^{-1}.

Reference Example 34

2-(5-chloro-2-nitrobenzyl)-3-hydroxypropyl-1-propionate



A mixture of 2- (5-chloro-2-nitrobenzyl)-1,3-propanediol-1-propionate (20 mg), Lipase PS (amano pharmaceuticals; 20 mg) and water(0.1 ml) was shaked in IPE (2.0 ml) at 35°C for 24 hours. High-performance chromatography analysis was performed on the reaction solution. According to the analysis, the yield of monoacyl body was 67% and the enantiomer excess was 91% ee.

HPLC condition: column; CHIRALPAK AD (Daicel chemical industries)

mobile phase; hexane/2-propanol (925/75)

velocity; 0.8 ml/min

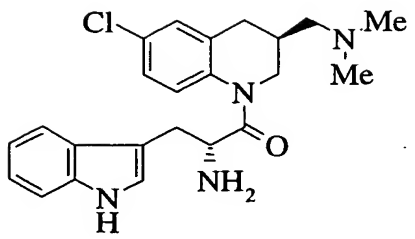
temperature; room temperature

detection; UV (225 nm)

retention time; 21, 24 min.

Reference Example 35

1-[2-(R)-amino-3-(indol-3-yl)propanoyl]-6-chloro-3-(S)-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroquinoline



The title compound was obtained according to the same method as Reference Example 11.

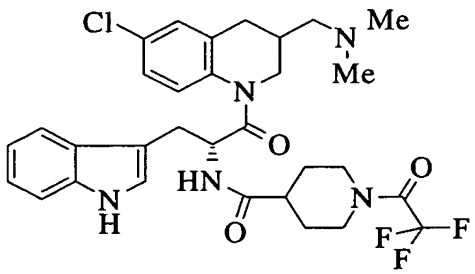
IR(KBr): 3280, 2928, 1653, 1487, 1356, 1235, 1098, 743 cm^{-1}.

$[\alpha]_D^{20}$ = -240° (c = 0.501, methanol).

MASS (APCIMASS): m/z 411 [$(M+H)^+$].

Reference Example 36

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-trifluoroacetyl-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



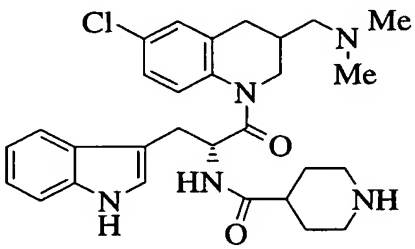
The title compound was obtained according to the same method as Example 1.

IR(KBr): 3308, 2946, 1694, 1634, 1487, 1175, 1144, 745 cm^{-1}.

MASS (APCIMASS), m/z 618[$(M+H)^+$].

Reference Example 37

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



To a solution of 3-(R,S)-(N,N-dimethylamino)methyl-6-

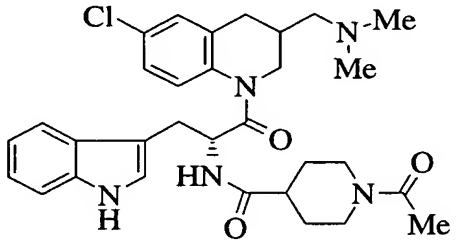
chloro-1-[3-(indol-3-yl)-2-[(R)-1-trifluoroacetyl-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline (200 mg) in methanol (4 ml) was added an aqueous solution of 10% potassium carbonate (2 ml). The mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure. To the residue was added water. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried and concentrated under reduced pressure. The title compound was obtained as amorphous powders (155 mg).

IR(KBr):3279, 2944, 2822, 1636, 1487, 1233, 743 cm^{-1}.

MASS (APCIMASS), m/z 522[$(M+H)^+$].

Reference Example 38

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-acetyl-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

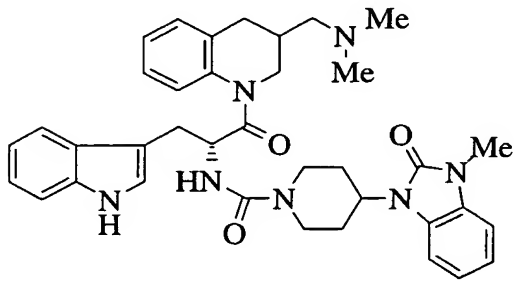


To a solution of 3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline (150 mg) in ethyl acetate (1.5 ml) was added a saturated aqueous solution of sodium hydrogencarbonate. Under ice cooling, acetyl chloride (0.031 ml) was dropwise added thereto. The mixture was stirred for 30 minutes. Then, the ethyl acetate layer was separated. The ethyl acetate layer was washed with saturated brine, dried and concentrated under reduced pressure. The title compound was obtained as amorphous powders (80 mg).

Reference Example 39

3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-4-(3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-

yl)piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



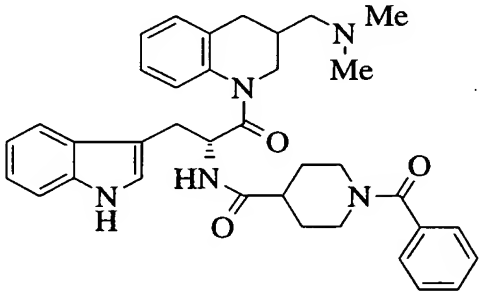
The title compound was obtained according to the same method as the later described Example 21.

IR(KBr): 3252, 2936, 1694, 1634, 1495, 1435, 1246, 750 cm^{-1}.

MASS (APCIMASS), m/z 634[$(M+H)^+$].

Reference Example 40

1-benzoyl-N-[(1R)-2-[3-(dimethylamino)methyl]-1,2,3,4-tetrahydro-1-quinolinyl]-1-(indol-3-ylmethyl)-2-oxoethyl]-4-piperidine carboxamide

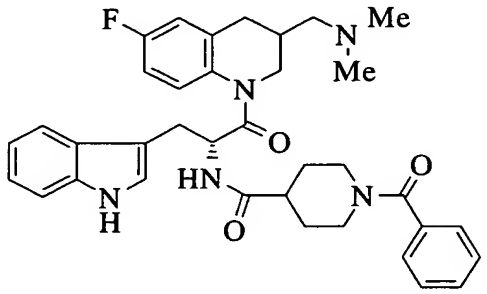


To a mixture of 1-[2-(R)-amino-3-(indol-3-yl)propanoyl]-3-(R,S)-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroquinoline (151 mg), 1-benzoyl-4-piperidinecarboxylic acid (104 mg) and HOBt (68 mg) in acetonitrile (5 ml) was added WSC (84 mg) and triethylamine (0.07 ml) at room temperature. The mixture was stirred at room temperature for 16 hours. Then, to the reaction solution was added an aqueous solution of 10% potassium carbonate. The solution was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent: ethyl acetate/methanol = 10/1) and the title compound was obtained as amorphous powders (205 mg).

IR(KBr): 3285, 2942, 1634, 1493, 1447, 743, 708 cm^{-1}.

Example 1

3-(R,S)-(N,N-dimethylamino)methyl-6-fluoro-1-[3-(indol-3-yl)-2-[(R)-1-benzoyl-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



To a solution of 1-[2-(R)-amino-3-(indol-3-yl)propanoyl]-3-(R,S)-(N,N-dimethylamino)methyl-6-fluoro-1,2,3,4-tetrahydroquinoline (150 mg) in acetonitrile (3 ml) was added N-benzoylisonipecotic acid (115 mg), WSC (110 mg) and HOBt (61 mg). The mixture was stirred at room temperature for 3 hours. To the reaction solution was added a saturated aqueous solution of sodium hydrogen carbonate. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent; ethyl acetate - ethyl acetate/methanol = 10:1) and the title compound was obtained as amorphous powders (195 mg).

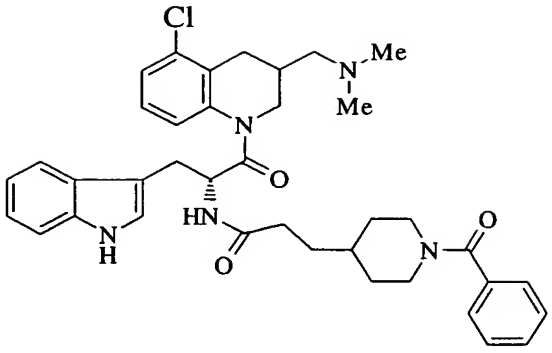
IR(KBr): 3289, 2942, 1632, 1497, 1447, 743, 708 cm^{-1}.

MASS (APCIMASS), m/z 610[$(M+H)^+$].

The following compounds mentioned in Examples 2-7 were synthesized by the same method as Example 1.

Example 2

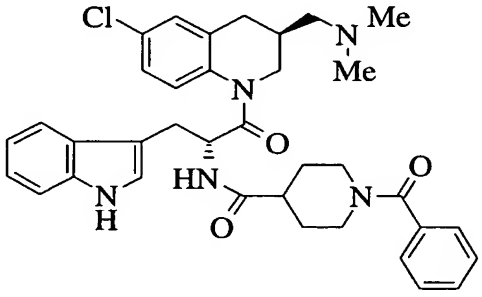
3-(1-benzoyl-4-piperidinyl)-N-[(1R)-2-[5-chloro-3-[(dimethylamino)methyl]-1,2,3,4-tetrahydro-1-quinolinyl]-1-(1-indol-3-ylmethyl)-2-oxoethyl]propanamide



IR(KBr): 3260, 2932, 1636, 1456, 1281, 741, 710 cm^{-1}.

Example 3

6-chloro-3-(S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-1-benzoyl-4-piperidinocarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



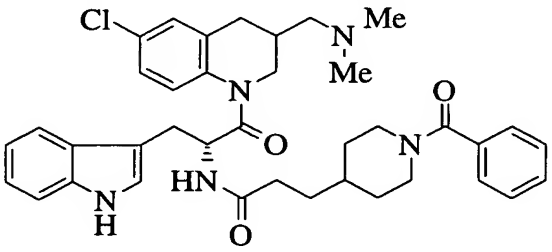
IR(KBr): 3283, 2942, 1624, 1487, 1447, 1281, 1231, 1096, 743 cm^{-1}.

$[\alpha]_D^{20}$ = -153° (c = 0.496, methanol).

MASS (APCIMASS): m/z 626 [$(M+H)^+$].

Example 4

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-benzoyl-4-piperidinoethylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

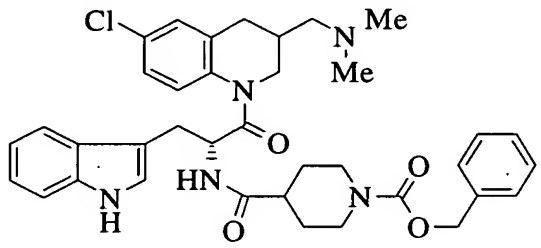


IR(KBr): 3287, 2934, 2863, 1634, 1487, 1445, 1279, 743 cm^{-1}.

MASS (APCIMASS), m/z 654[$(M+H)^+$].

Example 5

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-benzyloxycarbonyl-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

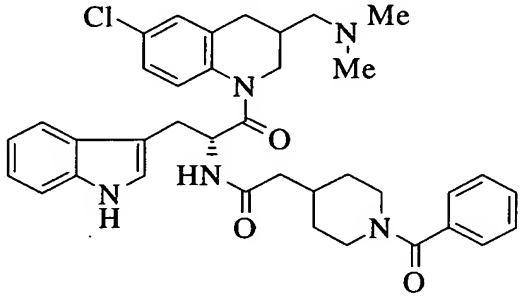


IR(KBr): 3308, 2948, 1686, 1634, 1487, 1433, 1215, 743 cm^{-1}.

MASS (APCIMASS), m/z 656[$(M+H)^+$].

Example 6

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-benzoyl-4-piperidinomethylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

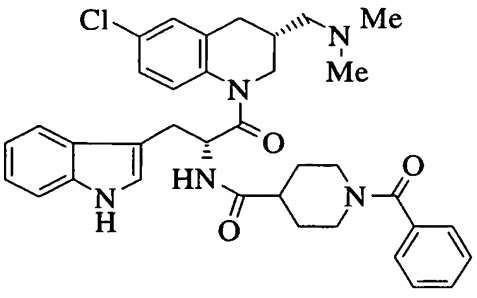


IR(KBr):3283, 2936, 1634, 1487, 1445, 1279, 743 cm^{-1}.

MASS (APCIMASS), m/z 640[$(M+H)^+$].

Example 7

3-(R)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-benzoyl-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



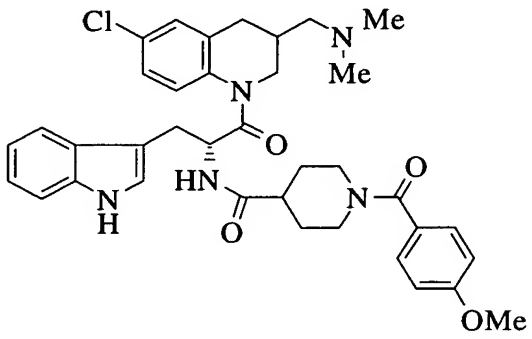
IR(KBr): 3289, 2944, 1634, 1487, 1435, 1280, 1094, 743 cm^{-1}.

MASS (APCIMASS), m/z 626[$(M+H)^+$].

$[\alpha]_D^{20}$ = -147°(c=0.498% methanol)

Example 8

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(4-methoxybenzoyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



To a solution of 3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline (150 mg) in acetonitrile (3 ml) was added p-methoxy benzoic acid (57 mg), WSC (83 mg) and HOBt (46 mg). The mixture was stirred at room temperature for 2 hours. To the reaction solution was added a saturated aqueous solution of sodium hydrogen carbonate. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent; ethyl acetate/hexane = 1:4 - ethyl acetate/methanol = 20:1) and the title compound was obtained as amorphous powders (150 mg).

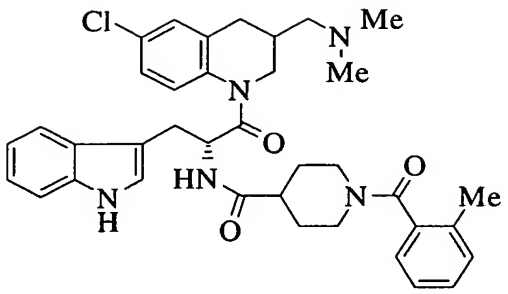
IR(KBr): 3289, 2942, 1634, 1613, 1487, 1439, 1250, 743 cm^{-1}.

MASS (APCIMASS), m/z 656[$(M+H)^+$].

The following compounds mentioned in Examples 9-20 were synthesized by the same method as Example 8.

Example 9

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(2-toluoyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

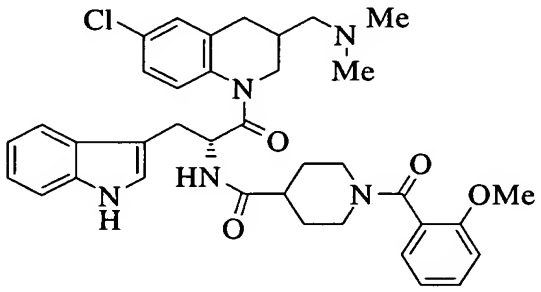


IR(KBr):3285, 2946, 1634, 1487, 1456, 1230, 743 cm^{-1}.

MASS (APCIMASS), m/z 640[$(M+H)^+$].

Example 10

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(2-methoxybenzoyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

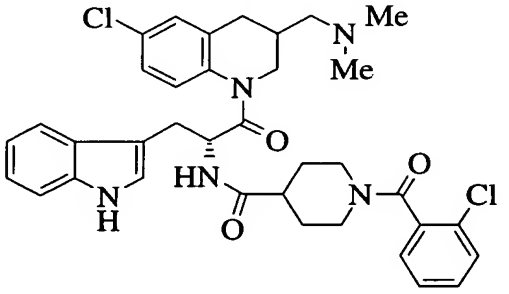


IR(KBr):3297, 2944, 1626, 1489, 1435, 1246, 743 cm^{-1}.

MASS (APCIMASS), m/z 656[$(M+H)^+$].

Example 11

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(2-chlorobenzoyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



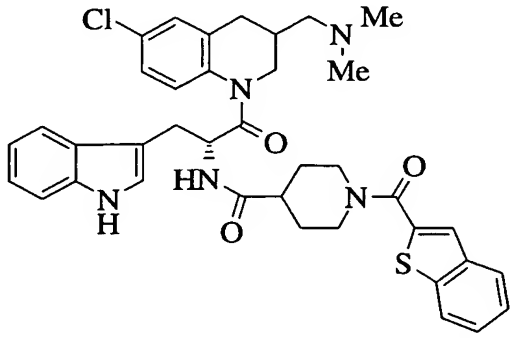
IR(KBr):3304, 2944, 2861, 1634, 1487, 1445, 743 cm^{-1}.

MASS (APCIMASS), m/z 660[$(M+H)^+$].

Example 12

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-

[(R)-1-(2-benzothiophenecarbonyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

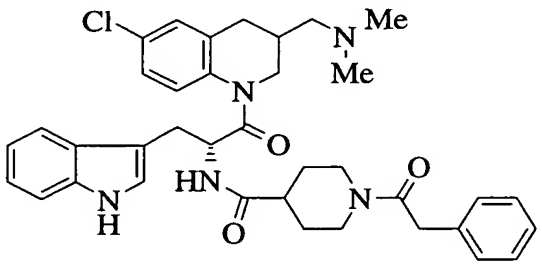


IR(KBr):3289, 2944, 1632, 1487, 1456, 1273, 743 cm^{-1}.

MASS (APCIMASS), m/z 682[$(M+H)^+$].

Example 13

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(2-phenylacetyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

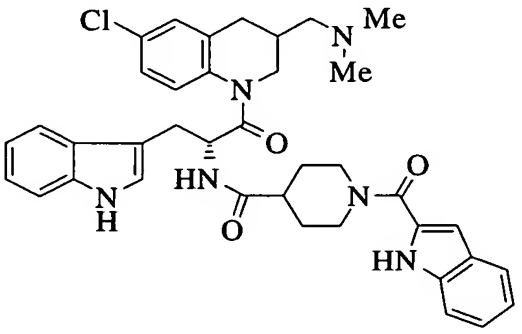


IR(KBr): 3297, 2944, 1632, 1487, 1456, 1100, 741, 729 cm^{-1}.

MASS (APCIMASS), m/z 640[$(M+H)^+$].

Example 14

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(2-indolecarbonyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

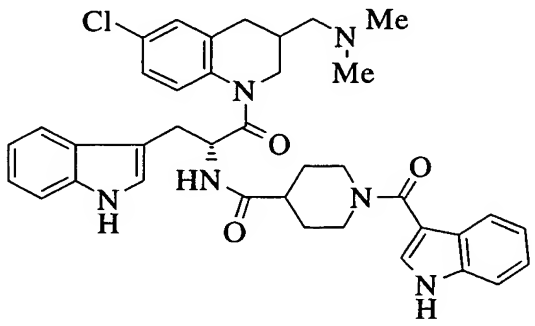


IR(KBr): 3283, 2938, 1638, 1601, 1528, 1487, 1439, 745 cm^{-1}.

MASS (APCIMASS), m/z 665[$(M+H)^+$].

Example 15

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(3-indolecarbonyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

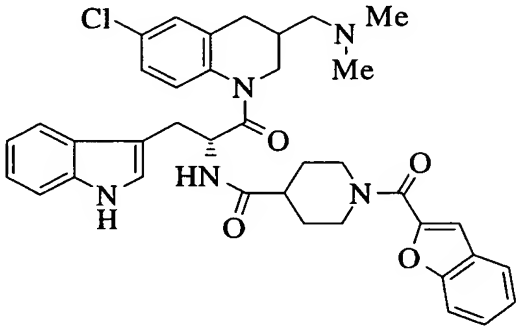


IR(KBr): 3283, 2942, 1636, 1595, 1532, 1487, 1439, 743 cm^{-1}.

MASS (APCIMASS), m/z 665[$(M+H)^+$].

Example 16

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(2-benzofurancarbonyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

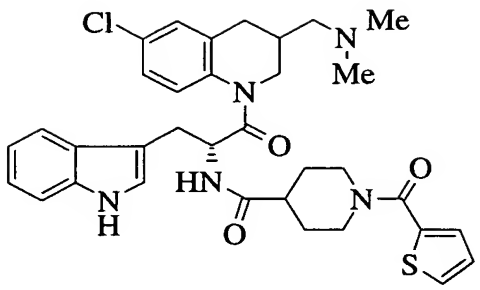


IR(KBr):3285, 2938, 1632, 1487, 1437, 1177, 745 cm^{-1}.

MASS (APCIMASS), m/z 666[$(M+H)^+$].

Example 17

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(2-thiophenecarbonyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

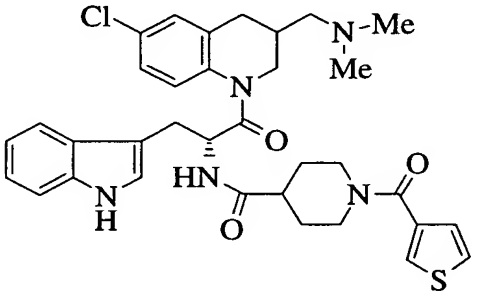


IR(KBr): 3291, 2938, 1636, 1522, 1487, 1439, 1273, 741 cm^{-1}.

MASS (APCIMASS), m/z 632[$(M+H)^+$].

Example 18

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(3-thiophenecarbonyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

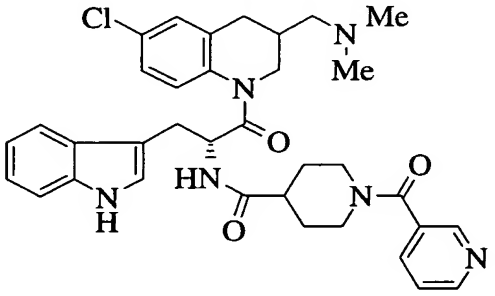


IR(KBr): 3293, 2942, 1634, 1526, 1487, 1445, 1275, 741 cm^{-1}.

MASS (APCIMASS), m/z 632[$(M+H)^+$].

Example 19

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-[(R)-1-(3-pyridinyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



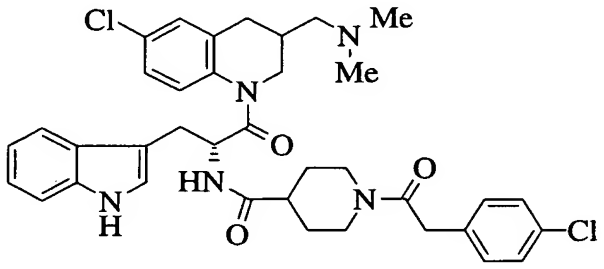
IR(KBr):3293, 2944, 1634, 1487, 1441, 1283, 741 cm^{-1}.

MASS (APCIMASS), m/z 627[$(M+H)^+$].

Example 20

3-(R,S)-(N,N-dimethylamino)methyl-6-chloro-1-[3-(indol-3-yl)-2-

[(R)-1-(2-(4-chlorophenyl)acetyl)-4-piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

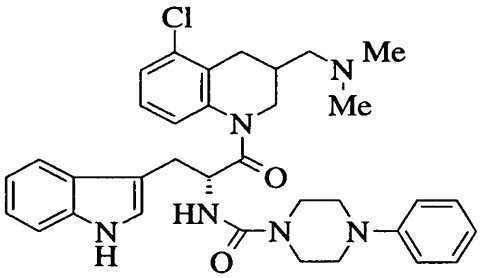


IR(KBr):3297, 2969, 1634, 1487, 1456, 1092, 743 cm^{-1}.

MASS (APCIMASS), m/z 674[$(M+H)^+$].

Example 21

5-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-(4-phenylpiperazin-1-yl)carbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



To a solution of 1-[2-(R)-amino-3-(indol-3-yl)propanoyl]-5-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydroquinoline (154 mg) and N-ethyldiisopropylamine (0.07 ml) in acetonitrile (5 ml) was added N,N'-disuccinimidyl carbonate (96 mg). The mixture was stirred at room temperature for 30 minutes. To the reaction solution was added 1-phenylpiperazine (62 mg) and a solution of N-ethyldiisopropylamine (0.07 ml) in acetonitrile (5 ml). Furthermore, the reaction solution was stirred at room temperature for 3 hours. Then, to the reaction solution was added an aqueous solution of 10% potassium carbonate. The reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by alumina column chromatography

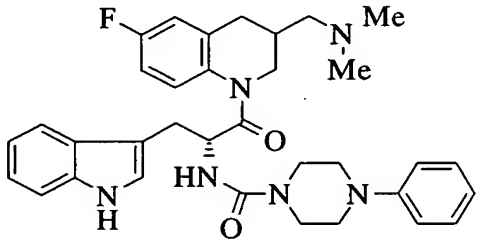
(developing solvent; ethyl acetate/methanol = 10/1) and the title compound was obtained as amorphous powders (136 mg).

IR(KBr):3266, 2971, 2820, 1636, 1458, 1233, 743 cm^{-1}

The following compounds mentioned in Examples 22-25 were synthesized according to the same method as Example 21.

Example 22

3-(R,S)-(N,N-dimethylamino)methyl-6-fluoro-1-[3-(indol-3-yl)-2-[(R)-(4-phenylpiperazin-1-yl)carbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

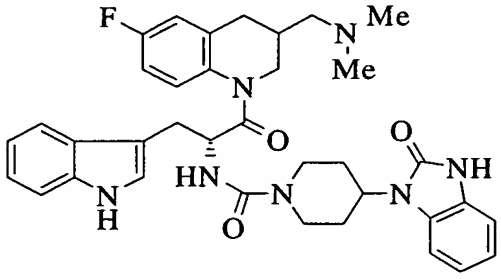


IR(KBr):3268, 2857, 2822, 1632, 1497, 1233, 760 cm^{-1}.

MASS (APCIMASS), m/z 583[$(M+H)^+$].

Example 23

3-(R,S)-(N,N-dimethylamino)methyl-6-fluoro-1-[3-(indol-3-yl)-2-[(R)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

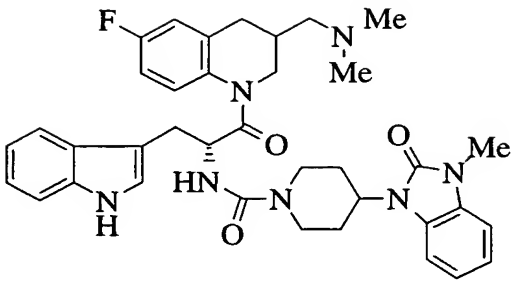


IR(KBr):3252, 2940, 1694, 1632, 1495, 1244, 756 cm^{-1}.

MASS (APCIMASS), m/z 638[$(M+H)^+$].

Example 24

3-(R,S)-(N,N-dimethylamino)methyl-6-fluoro-1-[3-(indol-3-yl)-2-[(R)-4-(3-methyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidylcarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline

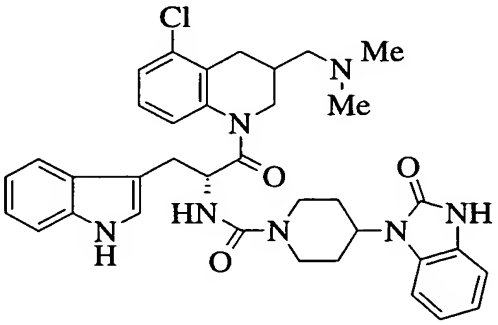


IR(KBr): 3254, 2938, 1694, 1634, 1497, 1435, 1242, 752 cm^{-1}.

MASS (APCIMASS), m/z 652[$(M+H)^+$].

Example 25

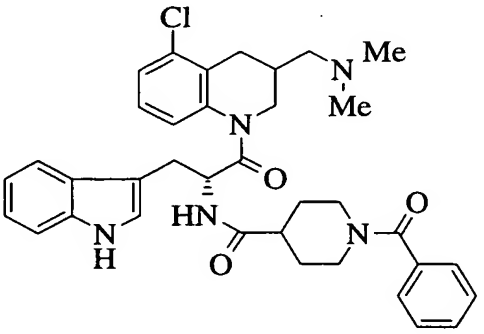
5-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidinocarbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline



IR(KBr): 3272, 2971, 1694, 1634, 1483, 1464, 1246, 741 cm^{-1}.

Example 26

1-benzoyl-N-[(R)-2-[5-chloro-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinolin-1-yl]-1-[3-(indol-3-yl)propanoyl]-4-piperidinecarboxamide



To a mixture of 1-[2-(R)-amino-3-(indol-3-yl)propanoyl]-5-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1,2,3,4-

tetrahydroquinoline (151 mg), 1-benzoyl-4-piperidinecarboxylic acid (94 mg) and HOBt (60 mg) in acetonitrile (5 ml) was added WSC (101 mg) at room temperature. The mixture was stirred at room temperature for 16 hours. Then, to the reaction solution was added an aqueous solution of 10% potassium carbonate. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by alumina column chromatography (developing solvent: ethyl acetate/methanol = 10/1) and the title compound was obtained as amorphous powders (218 mg).

IR(KBr): 3283, 2934, 1634, 1281, 739, 708 cm^{-1}.

Formulation Example 1

(1)	Compound obtained in Example 1	50.0 mg
(2)	Lactose	34.0 mg
(3)	Corn Starch	10.6 mg
(4)	Corn Starch (pasty)	5.0 mg
(5)	Magnesium Stearate	0.4 mg
(6)	Carboxymethyl Cellulose Calcium	20.0 mg
	Total	120.0 mg

The above (1) to (6) were admixed in an ordinary manner, and tabletted using a tabletting machine, to obtain tablets.

Experimental Example 1

The followings are some examples of the pharmacological actions of the compounds of the present invention, which should not be construed as being limiting to them. The gene manipulation using *E. coli* was conducted in accordance with the method described in the 1989 Edition of Molecular Cloning.

(1) Cloning of human somatostatin receptor protein subtype 4 (hSSTR4) DNA

DNA oligomers S4-1 and S4-2 were synthesized based on the known human SSTR4 DNA sequence (Rohrer etal., Proc. Natl, Acad. Sci., USA 90, 4196-4200, 1993). The sequence of S4-1 is 5'-GGCTCGAGTCACCATGAGCGCCCCCTCG-3' (Sequence No. 1) and that of S4-

2 is 5'-GGGCTCGAGCTCCTCAGAAGGTGGTGG-3' (Sequence No. 2).

Human chromosomal DNA (Clonetech Inc. Catalog No. CL6550-1) was used as the template. To 0.5 ng of said DNA was added 25 pmol of each of the above-mentioned DNA oligomers and the polymerase chain reaction was carried out using 2.5 units of PfuDNA polymerase (Strata gene). The composition of the reaction mixture was in accordance with the directions attached to said Pfu DNA polymerase.

The conditions of the reaction were as follows: One cycle consisting of the reactions at 94°C for 1 minute, at 66°C for 1 minute and at 75°C for 2 minutes, and 35 cycles were repeated. The reaction mixture was subjected to electrophoresis on 1% agarose gel to find that the DNA fragments of the intended size (about 1.2 kb) were specifically amplified. Said DNA fragments were recovered from the agarose gel in the usual manner and ligated to pUC118 cleaved at the Hinc II site to transform into the competent cells, *Escherichia coli* JM109. The transformant having plasmid containing said DNA fragments was selected out and the sequence of the inserted DNA fragments was confirmed by the automatic sequence analyzer employing fluorochroming, ALF DNA Sequencer (Pharmacia). As the results, the amino acid sequence expected from the nucleotide sequence was completely in agreement with the sequence described in the above-mentioned reports by Rohrer et al.

(2) Construction of the expression plasmid of human somatostatin receptor protein subtype 4 (hSSTR4) DNA

pAKKO-111 was used as the expression vector in CHO (Chinese Hamster Ovary) cells. pAKKO-111 was constructed as follows: The 1.4 kb DNA fragment containing SRα promoter and poly A appositional signal was obtained from pTB1417 described in JP-A-H5(1993)-076385 by the treatment with a restriction enzyme (Hind III) and a restriction enzyme (Cla I). On the other hand, the 4.5 kb DNA fragment containing dihydrofolic acid reductase gene (dhfr) was obtained from pTB348 [Naruo, K. et al., Biochem.

Biophys. Res. Commun., 128, 256-264, 1985] by the treatment with a restriction enzyme (Cla I) and a restriction enzyme (Sal I). These DNA fragments were treated with T4 polymerase to make the terminal blunt-ended and ligated with T4 ligase to construct pAKKO-111 plasmid.

Then, 5 μg of the plasmid having human SSTR4 DNA fragment was digested with a restriction enzyme (XhoI) and subjected to electrophoresis on 1% agarose gel to recover the 1.2 kb DNA fragment encoding human SSTR4. Next, 1 μg of the above-mentioned expression vector pAKKO-111 (5.5 kb) was digested with Sal I to prepare the cloning site for insertion of human SSTR4 DNA fragment. Said expression vector fragment and the 1.2 kb DNA fragment were ligated with T4DNA ligase. The reaction mixture was introduced into *E. coli* JM 109 by the calcium chloride method to obtain the expression plasmid pA1-11-hSSTR4 in which human SSTR4 DNA fragment was inserted in regular direction against the promoter from the transformants. This transformant is expressed as *Escherichia coli* JM109/pA-1-11-hSSTR4.

(3) Transfection and expression of human somatostatin receptor protein subtype 4 (hSSTR4) DNA in CHO ($dhfr^-$) cells

1 x 10^6 CHO ($dhfr^-$) cells were cultured for 24 hours in HAM F12 medium containing 10% bovine fetal serum on a laboratory dish of 8 cm in diameter. The cells were transfected by 10 μg of the human SSTR4 DNA expression plasmid, pA-1-11-hSSTR4 obtained above using the calcium phosphate method (Cell Phect Transfection Kit; Pharmacia). The medium was switched to Dulbecco's Modified Eagle Medium (DMEM) containing 10% dialyzed bovine fetal serum 24 hours after the transfection to select the colony-forming cells (i.e. $dhfr^+$ cells) in this medium. Further, the selected cells were cloned from a single cell by the limiting dilution method and the somatostatin receptor protein expression activity of these cells was measured as follows: Human SSTR4 receptor expression cell strain was diluted with a

buffer solution for assay [50 mM of Tris hydrochloride, 1 mM of EDTA, 5 mM of magnesium chloride, 0.1% of BSA, 0.2 mg/ml of bacitracin, 10 μg/ml of leupeptin, 1 μg/ml of pepstatin and 200 units/ml of aprotinin (pH 7.5)] to adjust the cell number to 2 x 10^4/200 μl. 200 μl of the dilution was placed in a tube and to this was added 2 μl of 5 nM [^{125}I]-somatostatin-14 (2000 Ci/mmol, Amersham). The mixture was incubated at 25°C for 60 minutes. For measurement of non-specific binding (NSB), the tube to which 2 μl of somatostatin-14 (10^{-4} M) was added was also incubated. To the tube was added 1.5 ml of a buffer solution for washing [50 mM of Tris-hydrochloride, 1 mM of EDTA and 5 mM of magnesium chloride (pH 7.5)] and the mixture was filtered by GF/F glass fiber filter paper (Whatman) and washed further with 1.5 ml of the same buffer solution. The amount of [^{125}I] of the filter was measured by a γ-counter. Thus, a highly somatostatin-binding cell strain, hSSTR4-1-2, was selected.

(4) Cloning of rat somatostatin receptor protein subtype 4 (rSSTR4) DNA

DNA oligomers S4-3 and S4-4 were synthesized based on the known rat SSTR4 DNA sequence (Bito.H etal., J. Biol. Chem., 269, 12722-12730, 1994).

The sequence of S4-3 is 5'-AAGCATGAACACGCCTGCAACTC-3' (Sequence No. 3) and that of S4-4 is 5'-GGTTTTCAGAAAGTAGTGGTCTT-3' (Sequence No. 4).

As the template, a chromosomal DNA prepared from Sprague-Dawley rats by using Easy-DNA™ KIT (Invitrogen) was used. To 0.5 ng of said DNA was added 25 pmol of each of the above-mentioned DNA oligomers and the polymerase chain reaction was carried out using TaKaRa LAPCR KIT (TaKaRa).

The conditions of the reaction were as follows: One cycle consisting of the reactions at 95°C for 30 seconds, at 65°C for 2 minutes and 30 seconds, and 30 cycles were repeated. The reaction mixture was subjected to electrophoresis on 1% agarose gel to find that the DNA fragments of the intended size (about

1.2 kb) were specifically amplified. Said DNA fragments were recovered from the agarose gel in the usual manner and ligated to a vector (pCR™ 2.1 (Trade name)) of ORIGINALTA CLONINGKIT (Invitrogen) to transform into the competent cells, *Escherichia coli* JM109. The transformant having plasmid containing said DNA fragments was selected out and the sequence of the inserted DNA fragments was confirmed by the automatic sequence analyzer employing fluorochroming, ALF DNA Sequencer (Pharmacia). As the results, the amino acid sequence expected from the nucleotide sequence was completely in agreement with the sequence described in the above-mentioned reports by Bito. H et al.

(5) Construction of the expression plasmid of rat somatostatin receptor protein subtype 4 (rSSTR4) DNA

pAKKO-111 was used as the expression vector in CHO cells. 5 μg of the plasmid having rat SSTR4 DNA fragment obtained above was digested with a restriction enzyme (EcoRI), treated with T4 DNA polymerase, and subjected to electrophoresis on 1% agarose gel to recover the 1.2 kb DNA fragment encoding rat SSTR4. Next, 1 μg of the above-mentioned expression vector pAKKO-111 (5.5 kb) was digested with a restriction enzyme (ClaI), treated with T4 DNA polymerase and Alikaline Phosphatase, to prepare the cloning site for insertion of rat SSTR4 DNA fragment. Said expression vector fragment and the 1.2 kb DNA fragment were ligated with T4 DNA ligase. The reaction mixture was introduced into *E. coli* JM 109 by the calcium chloride method to obtain the expression plasmid pA1-11-rSSTR4 in which rat SSTR4 DNA fragment was inserted in regular direction against the promoter from the transformants. This transformant is expressed as *Escherichia coli* JM109/pA-1-11-rSSTR4.

(6) Transfection and expression of rat somatostatin receptor protein subtype 4 (rSSTR4) DNA in CHO ($dhfr^-$) cells

1×10^6 CHO ($dhfr^-$) cells were cultured for 24 hours in α-MEM medium (containing ribonucleoside and deoxynucleoside) containing 10% bovine fetal serum on a laboratory dish of 8 cm

in diameter. The cells were transfected by 10 μg of the rat SSTR4 DNA expression plasmid 1 pA-1-11-rSSTR4 obtained above using the calcium phosphate method (Cell Phect Transfection Kit; Pharmacia). The medium was switched to α-MEM medium (free of ribonucleoside and deoxynucleoside) containing 10% dialyzed bovine fetal serum 24 hours after the transfection to select the colony-forming cells (i.e. $dhfr^+$ cells) in this medium. Further, the selected cells were cloned from a single cell by the limiting dilution method and the somatostatin receptor protein expression activity of these cells was measured by the binding method mentioned above. Thus, a highly somatostatin-binding cell strain, rSSTR4-20-25, was selected.

(7) Preparation of CHO cell membrane fractions containing somatostatin receptor 4

Human and rat somatostatin receptor 4 expressing CHO cell strain, hSSTR4-1-2 or rSSTR4-20-25 (1×10^9) was floated on a phosphate buffered saline supplemented with 5 mM EDTA (PBS-EDTA) and centrifuged. To the cell pellets was added 10 ml of a homogenate buffer for cells (10 mM $NaHCO_3$, 5 mM EDTA, pH 7.5), which was homogenated using a Politron homogenizer. The supernatant obtained by centrifugation at 400 x g for 15 minutes was further centrifuged at 10,000 μg for 1 hour to give a precipitate of the membrane fraction. The precipitates were suspended in 2 ml of a buffer solution for assay [25 mM of Tris-HCl, 1 mM of EDTA (Ethylenediaminetetraacetic Acid), 0.1% of BSA (Bovine Serum Albumin), 0.25 mM of PMSF (Phenylmethylsulfonyl Fluoride), 1 μg/ml pepstatin, 20 μg/ml leupeptin, 10 μg/ml Phosphoramidone, pH7.5], which was centrifuged at 100,000 x g for 1 hour. The membrane fraction recovered as precipitates was suspended again in 20 ml of the buffer solution for assay, which was placed in tubes and stored at -80°C. The suspension was thawed and used at every use.

Experimental Example 2

(1) Cloning of human somatostatin receptor protein subtype

1 (SSTR1) DNA

DNA oligomers S1-1 and S1-2 were synthesized based on the known human SSTR1 cDNA sequence (Proc. Natl. Acad. Sci., USA vol.89, p.251-255, 1992). The sequence of S1-1 is 5'-GGTCGACCTCAGCT AGGATGTTCCCCAATG-3' (Sequence No. 5) and that of S1-2 is 5'-GGTCGACCCGGGCTCAGAGCGTCGTGAT-3' (Sequence No. 6). Human chromosomal DNA (Clonetech Inc. Catalog No. CL 6550-1) was used as the template. To 0.5 ng of said DNA was added 25 pmol of each of the above-mentioned DNA oligomers and the polymerase chain reaction was carried out using 2.5 units of Pfu DNA polymerase (Stratagene). The composition of the reaction mixture was in accordance with the directions attached to said Pfu DNA polymerase. The conditions of the reaction were as follows: One cycle consisting of the reactions at 94°C for 1 minute, at 63°C for 1 minute and at 75°C for 2 minutes, and 35 cycles were repeated. The reaction mixture was subjected to electrophoresis on 1% agarose gel to find that the DNA fragments of the intended size (about 1.2 kb) were specifically amplified. Said DNA fragments were recovered from the agarose gel in the usual manner and ligated to pUC118 cleaved at the Hinc II site to transform into the competent cells, *Escherichia coli* JM109. The transformant having plasmid containing said DNA fragments was selected out and the sequence of the inserted DNA fragments was confirmed by the automatic sequence analyzer employing fluorochroming, ALF DNA Sequencer (Pharmacia). As the results, the amino acid sequence expected from the nucleotide sequence was completely in agreement with the sequence described in the above-mentioned literature.

(2) Construction of the expression plasmid of human somatostatin receptor protein subtype 1 (SSTR1) DNA

pAKKO-111 was used as the expression vector in CHO (Chinese Hamster Ovary) cells. PAKKO-111 was constructed as follows: The 1.4 kb DNA fragment containing SRα promoter and poly A appositional signal was obtained from pTB1417 described in JP-A-

H5 (1993)-076385 by treatment with Hind III and Cla I. On the other hand, the 4.5 kb DNA fragment containing dihydrofolic acid reductase (DHFR) gene was obtained from pTB348 [Biochem. Biophys. Res. Commun., 128, p.256-264, 1985] by treatment with Cla I and Sal I. These DNA fragments were treated with T4 polymerase to make the terminal blunt-ended and ligated with T4 ligase to construct pAKKO-111 plasmid. Then, 5 μg of the plasmid having human SSTR1 DNA fragment obtained under the above (1) was digested with the restriction enzyme Sal I and subjected to electrophoresis on 1% agarose gel to recover the 1.2 kb DNA fragment encoding human SSTR1. Next, 1 μg of the above-mentioned expression vector pAKKO-111 (5.5 kb) was digested with Sal I to prepare the cloning site for insertion of human SSTR1 DNA fragment. Said expression vector fragment and the 1.2 kb DNA fragment were ligated with T4 DNA ligase. The reaction mixture was introduced into *E. coli* JM 109 by the calcium chloride method to obtain the expression plasmid pA1-11-SSTR1 in which human SSTR1 DNA fragment was inserted in regular direction against the promoter from the transformants. This transformant is expressed as *Escherichia coli* JM109/pA-1-11-SSTR1.

(3) Transfection and expression of human somatostatin receptor protein subtype 1 (SSTR1) DNA in CHO ($dhfr^-$) cells

1×10^6 CHO ($dhfr^-$) cells were cultured for 24 hours in HAM F12 medium containing 10% bovine fetal serum on a laboratory dish of 8 cm in diameter. The cells were transfected by 10 μg of the human SSTR1 cDNA expression plasmid 1 pA-1-11-SSTR1, obtained under the above (2) using the calcium phosphate method (Cell Phect Transfection Kit: Pharmacia). The medium was switched to DMEM medium containing 10% dialyzed bovine fetal serum 24 hours after the transfection to select the colony-forming cells (i.e. DHFR+ cells) in this medium. Further, the selected cells were cloned from a single cell by the limiting dilution method and the somatostatin protein activity was measured as follows: Human SSTR cDNA expression cell strain was

diluted with a buffer solution for assay [50 mM of Tris hydrochloride, 1 mM of EDTA, 5 mM of magnesium chloride, 0.1% of BSA, 0.2 mg/ml of bacitracin, 10 μg/ml of leupeptin, 1 μg/ml of pepstatin and 200 units/ml of aprotinin (pH 7.5)] to adjust the cell number to 2×10^4/200 μl. 200 μl of the dilution was placed in a tube and to this was added 2 μl of 5 nM [^{125}I]-somatostatin-14 (2000 Ci/mmol, Amersham). The mixture was incubated at 25°C for 60 minutes. For measurement of non-specific binding (NSB), the tube to which 2 μl of somatostatin-14 (10^{-4} M) was added was also incubated. To the tube was added 1.5 ml of a buffer solution for washing [50 mM of Tris hydrochloride, 1 mM of EDTA and 5 mM of magnesium chloride (pH 7.5)] and the mixture was filtered by GF/F glass fiber filter paper (Whatman) and washed further with 1.5 ml of the same buffer solution. The amount of [^{125}I] of the filter was measured by a γ-counter. Thus, a highly somatostatin-binding cell strain, SSTR1-8-3, was selected.

(4) Cloning of human somatostatin receptor protein subtype 2 (SSTR2) DNA

DNA oligomers PT-1 and PT-2 were synthesized based on the known human SSTR2c DNA sequence (Proc. Natl. Acad. Sci., USA vol.89, p.251-255, 1992). The sequence of PT-1 is 5'-GGTCGACACCATGGACATGGCGGATGAG-3' (Sequence No. 7) and that of PT-2 is 5'-GGTCGACAGTTCAGATACTGGTTTGG-3' (Sequence No. 8). Human pituitary gland cDNA (Clonetech Inc. Catalog No. 7173-1) was used as the template. To 1 ng of said cDNA was added 25 pmol of each of the above-mentioned DNA oligomers and the polymerase chain reaction was carried out using 2.5 units of Taq DNA polymerase (TaKaRa Shuzo). The composition of the reaction mixture was in accordance with the directions attached to said Taq DNA polymerase. The conditions of the reaction were as follows: One cycle consisting of the reactions at 94°C for 30 seconds, at 52°C for 20 seconds and at 72°C for 60 seconds, and 30 cycles were repeated. The reaction mixture was subjected to electrophoresis on 1% agarose gel to find that the DNA fragments

of the intended size (about 1.1 kb) was specifically amplified. Said DNA fragments were recovered from the agarose gel in the usual manner and ligated to pUC118 cleaved at the Hinc II site to transform into the competent cells, *Escherichia coli* JM109. Two strains (No. 5 and No. 7) of the transformant having plasmid containing said DNA fragments were selected out and the sequence of the inserted DNA fragments was confirmed by the automatic sequence analyzer employing fluorochroming, 373A DNA Sequencer (Applied Biosystem). As the results, point mutation was confirmed at one site between Sal I and Bst PI in the sequence of the 770 base fragment of No. 5 strain, and point mutation was also confirmed at one site between Bst PI and Sal I in the sequence of the 360 base fragment of No. 7 strain. Therefore, the fragments remaining after removing the Bst PI-Sal I fragment of No. 5 strain and the Bst PI-Sal I fragment of No. 7 strain were purified by electrophoresis on agarose to construct a plasmid in which these fragments were ligated by the ligation reaction. Confirmation of the insertion sequence of the DNA fragment of this plasmid revealed that it was completely in agreement with the sequence described in the above literature.

(5) Construction of the expression plasmid of human somatostatin receptor protein subtype 2 (SSTR2) DNA

pAKKO-111 mentioned under the above (2) was used as the expression vector in CHO (Chinese Hamster Ovary) cells. 5 μg of the plasmid having human SSTR2 cDNA fragment obtained under the above (4) was digested with the restriction enzyme Sal I and subjected to electrophoresis on 1% agarose gel to recover the 1.1 kb DNA fragment encoding human SSTR2. Next, 1 μg of the above-mentioned expression vector pAKKO-111 (5.5 kb) was digested with Sal I to prepare the cloning site for insertion of human SSTR2 DNA fragment. Said expression vector fragment and the 1.1 kb DNA fragment were ligated with T4 DNA ligase. The reaction mixture was introduced into *E. coli* JM 109 by the calcium chloride method to obtain the expression plasmid pAC01

in which human SSTR2 DNA fragment was inserted in regular direction against the promoter from the transformants. This transformant is expressed as *Escherichia coli* JM109/pAC-01.

(6) Transfection and expression of human somatostatin receptor protein subtype 2 (SSTR2) DNA in CHO ($dhfr^-$) cells

1×10^6 CHO ($dhfr^-$) cells were cultured for 24 hours in HAM F12 medium containing 10% bovine fetal serum on a laboratory dish of 8 cm in diameter. To the cells was transfected 10 μg of the human SSTR2 cDNA expression plasmid, pA-C01, obtained under the above (5) by the calcium phosphate method (Cell Phect Transfection Kit: Pharmacia). The medium was switched to DMEM medium containing 10% dialyzed bovine fetal serum 24 hours after the transfection to select the colony-forming cells (i.e. $DHFR^+$ cells) in this medium. Further, the selected cells were cloned from a single cell by the limiting dilution method and a cell strain which highly expresses human SSTR2, SSTR2-HS5-9, was selected.

(7) Cloning of human somatostatin receptor protein subtype 3 (SSTR3) DNA

DNA oligomers S3-1 and S3-2 were synthesized based on the known human SSTR3c DNA sequence (Mol. Endocrinol., vol.6, p.2136-2142, 1992). The sequence of S3-1 is 5'-GGTCGACCTCAACCATGGACATGCTTCATC-3' (Sequence No. 9) and that of S3-2 is 5'-GGTCGACTTTCCCCAGGCCCCTACAGGTA-3' (Sequence No. 10). Human chromosomal DNA (Clone Tech Inc. Catalog No. CL6550-1) was used as the template. To 0.5 ng of said DNA was added 25 pmol of each of the above-mentioned DNA oligomers and the polymerase chain reaction was carried out using 2.5 units of Pfu DNA polymerase (Strata gene). The composition of the reaction mixture was in accordance with the directions attached to said Pfu DNA polymerase. The conditions of the reaction were as follows: One cycle consisting of the reactions at 94°C for 1 minute, at 63°C for 1 minute and at 75°C for 2 minutes, and 35 cycles were repeated. The reaction mixture was subjected to

electrophoresis on 1% agarose gel to find that the DNA fragments of the intended size (about 1.3 kb) was specifically amplified. As the results, the amino acid sequence expected from the nucleotide sequence was completely in agreement with the sequence described in the above-mentioned literature.

(8) Construction of the expression plasmid of human somatostatin receptor protein subtype 3 (SSTR3) DNA

pAKKO-111 mentioned under the above (2) was used as the expression vector in CHO cells. 5 μg of the plasmid having human SSTR3 DNA fragment obtained under the above (7) was digested with the restriction enzyme Sal I and subjected to electrophoresis on 1% agarose gel to recover the 1.3 kb DNA fragment encoding human SSTR3. Next, 1 μg of the above-mentioned expression vector pAKKO-111 (5.5 kb) was digested with Sal I to prepare the cloning site for insertion of human SSTR3 DNA fragment. Said expression vector and the 1.3 kb DNA fragment were ligated with T4DNA ligase. The reaction mixture was introduced into *E. coli* JM 109 by the calcium chloride method to obtain the expression plasmid pA1-11-SSTR3 in which human SSTR3 DNA fragment was inserted in regular direction against the promoter from the transformants. This transformant is expressed as *Escherichia coli* JM109/pA-1-11-SSTR3.

(9) Transfection and expression of human somatostatin receptor protein subtype 3 (SSTR3) DNA in CHO ($dhfr^-$) cells

1×10^6 CHO ($dhfr^-$) cells were cultured for 24 hours in HAM F12 medium containing 10% bovine fetal serum on a laboratory dish of 8 cm in diameter. The cells were transfected by 10 μg of the human SSTR3 DNA expression plasmid, pA-1-11-SSTR3, obtained under the above (5) using the calcium phosphate method. The medium was switched to DMEM medium containing 10% dialyzed bovine fetal serum 24 hours after the transfection to select the colony-forming cells (i.e. $DHFR^+$ cells) in this medium. Further, the selected cells were cloned from a single cell by the limiting dilution method and the somatostatin receptor protein

expression activity of these cells was measured by the binding assay mentioned under the above (3). Thus, a highly somatostatin-binding cell strain, SSTR3-15-19, was selected.

(10) Cloning of human somatostatin receptor protein subtype (SSTR5) DNA

DNA oligomers S5-1 and S5-2 were synthesized based on the known human SSTR5c DNA sequence (Biochem Biophys. Res. Commun., vol.195, p.844-852, 1993). The sequence of S5-1 is 5'-GGTCGACCACCATGGAGCCCCTGTTCCC-3' (Sequence No. 11) and that of S5-2 is 5'-CCGTCGACACTCTCACAGCTTGCTGG-3' (Sequence No. 12). Human chromosomal DNA (Clonetech Inc. Catalog No. CL6550-1) was used as the template. To 0.5 ng of said DNA was added 25 pmol of each of the above-mentioned DNA oligomers and the polymerase chain reaction was carried out using 2.5 units of Pfu DNA polymerase (Stratagene). The composition of the reaction mixture was in accordance with the directions attached to PfuDNA polymerase. The conditions of the reaction were as follows: One cycle consisting of the reactions at 94°C for 1 minute, at 66°C for 1 minute and at 75°C for 2 minutes, and 35 cycles were repeated. The reaction mixture was subjected to electrophoresis on 1% agarose gel to find that the DNA fragments of the intended size (about 1.1 kb) were specifically amplified. Confirmation of the insertion sequence of said DNA fragment by the method mentioned under the above (1) revealed that the amino acid sequence expected from the nucleotide sequence was completely in agreement with the sequence described in the above-mentioned literature.

(11) Construction of the expression plasmid of human somatostatin receptor protein subtype 5 (SSTR5) DNA.

pAKKO-111 mentioned under the above (2) was used as the expression vector in CHO cells. 5 μg of the plasmid having human SSTR5 DNA fragment obtained under the above (10) was digested with the restriction enzyme Sal I and subjected to electrophoresis on 1% agarose gel to recover the 1.1 kb DNA

fragment encoding human SSTR5. Next, 1 μg of the above-mentioned expression vector pAKKO-111 (5.5 kb) was digested with Sal I to prepare the cloning site for insertion of human SSTR5 DNA fragment. Said expression vector fragment and the 1.1 kb DNA fragment were ligated with T4 DNA ligase. The reaction mixture was introduced into *E. coli* JM 109 by the calcium chloride method to obtain the expression plasmid pA1-11-SSTR5 in which human SSTR5 DNA fragment was inserted in regular direction against the promoter from the transformants. This transformant is expressed as *Escherichia coli* JM109/pA-1-11-SSTR5.

(12) Transfection and expression of human somatostatin receptor protein subtype 5 (SSTR5) DNA in CHO ($dhfr^-$) cells

1 x 10^6 CHO ($dhfr^-$) cells were cultured for 24 hours in HAM F12 medium containing 10% bovine fetal serum on a laboratory dish of 8 cm in diameter. To the cells was transfected 10 μg of the human SSTR5 cDNA expression plasmid, pA-1-11-SSTR5, obtained under the above (11) by the calcium phosphate method. The medium was switched to DMEM medium containing 10% dialyzed bovine fetal serum 24 hours after the transfection to select the colony-forming cells (i.e. $DHFR^+$ cells) in this medium. Further, the selected cells were cloned from a single cell by the limiting dilution method and the somatostatin receptor protein expression activity of these cells was measured by binding assay mentioned under the above (3). Thus, a highly somatostatin-biding cell strain, SSTR5-32-4, was selected.

Experimental Example 3

Measurement of the binding inhibition rate of ^{125}I-Somatostatin

The receptor binding inhibition rate (%) of the subject compound was calculated using each of the membrane fractions prepared in Experimental Examples 1 and 2.

The membrane fraction was diluted with a buffer solution for assay to adjust the concentration to 3 μg/ml. The diluate was placed in tubes each in quantity of 173 μl. To this were

simultaneously added 2 μl of a solution of a subject compound in DMSO and 25 μl of a 200 pM radioisotope-labeled somatostatin-14 (^{125}I-somatostatin-14: Amersham). For measurement of the maximum binding, a reaction mixture added with 2 μl of DMSO and 25 μl of a 200 pM ^{125}I-somatostatin was prepared. For measurement of non-specific binding, a reaction mixture added with 2 μl of a 100 μM somatostatin solution in DMSO and 25 μl of a 200 pM ^{125}I-somatostatin solution was prepared at the same time. The mixtures were allowed to react at 25°C for 60 minutes. Then, the reaction mixture was filtered by aspiration using a Whatman glass filter (GF-B) treated with polyethylenimine. After filtration, the radioactivity of ^{125}I-somatostatin-14 remaining on the filter paper was measured by a γ-counter. The binding inhibition rate (%) of each subject compound was calculated by the following formula:

(TB-SB)/(TB-NSB) x 100

SB: radioactivity when a compound was added

TB: maximum binding radioactivity

NSB: non-specific binding radioactivity

The binding inhibition rates were measured by changing the concentrations of the subject compound, and the 50% inhibiting concentration of the subject compound (IC_{50} value) was calculated by the Hill plots.

[Results]

	IC_{50} (nM)		
Example No	SSTR2	SSTR3	SSTR5
14	0.6	70	300

This shows that the compound (I) of the present invention and salts thereof have a binding inhibition effect on the human and rat somatostatin receptor.

【Effect of the Invention】

The compound of the present invention has an excellent somatostatin receptor binding inhibition action with low toxicity. Therefore, the compound of the present invention is useful for disorders of an intracellular signal transduction system (e.g., diseases accompanied by excess sthenia or suppression, etc.); diseases accompanied by disorders of regulating cell proliferation; diseases accompanied by disorders of production and/or secretion of hormones, growth factors, or physiologically active substances, etc.; in a mammal.

【Sequence Listing】

Sequence Listing

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<120> Amine Compounds

<130> A99181

<160> 12

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GGTCGACCAC CATGGAGCCC CTGTTCCC 28

<210> 12

<211> 26

<212> DNA

<213> Artificial Sequence

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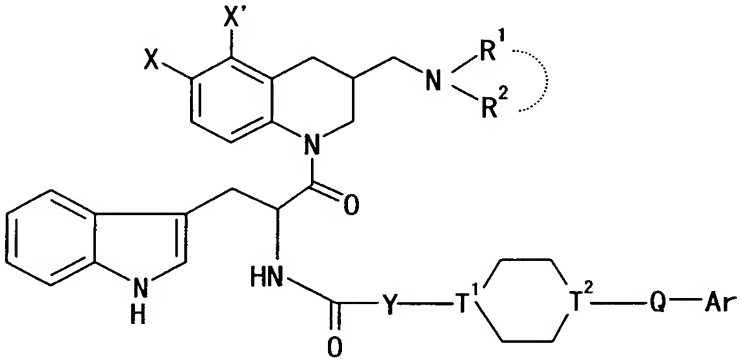
CCGTCGACAC TCTCACAGCT TGCTGG 26

【Document】 Abstract

【Summary】

【Problems】 Provision of a compound which has an excellent somatostatin receptor binding inhibition activity, and is useful for preventing and/or treating diseases associated with somatostatin.

【Solving Means】 A compound of the formula:



(I)

wherein X and X' are the same or different, and each represents a hydrogen atom, a fluorine atom or a chlorine atom, and at least one of X and X' represents a fluorine atom or a chlorine atom;

R^1 and R^2 represent a hydrogen atom or C_{1-6} alkyl optionally having substituents, or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring optionally having substituents;

Y and Q are the same or different, and each represents a bond or a spacer having a main chain of 1 to 6 atoms;

T^1 and T^2 are the same or different, and each represents CH or a nitrogen atom; and

Ar represents an aromatic group optionally having substituents;

provided that 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-(4-phenylpiperazin-1-yl)carbonylamino]propanoyl]-1,2,3,4-tetrahydroquinoline; 6-chloro-3-(R,S)-(N,N-dimethylamino)methyl-1-[3-(indol-3-yl)-2-[(R)-4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidinocarbonylamino]propanoyl]-1,2,3,4-

tetrahydroquinoline and 1-benzoyl-N-[(R)-2-[6-chloro-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinolin-1-yl]-1-[3-(indol-3-yl)propanoyl]-4-piperidinecarboxamide are excluded; or a salt thereof.

【Main Drawing】 None